No. 2014-1799, 2014-1800

United States Court of Appeals for the Federal Circuit

NOVARTIS PHARMACEUTICALS CORPORATION,
NOVARTIS AG, NOVARTIS PHARMA AG,
NOVARTIS INTERNATIONAL PHARMACEUTICAL LTD., AND
LTS LOHMANN THERAPIE-SYSTEME AG,
PLAINTIFFS-APPELLEES

v.

WATSON LABORATORIES, INC.,
WATSON PHARMA, INC., NKA ACTAVIS PHARMA, INC., AND
ACTAVIS, INC., FKA WATSON PHARMACEUTICALS, INC.,
DEFENDANTS-APPELLANTS

APPEAL FROM THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE
CASE NOS. 1:11-CV-01112-RGA & 1:13-CV-00371-RGA
JUDGE RICHARD G. ANDREWS

BRIEF FOR DEFENDANTS-APPELLANTS

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CERTIFICATE OF INTEREST

Counsel for Defendants-Appellants certifies the following:

1. The full name of every party or amicus represented by us is:

Watson Laboratories, Inc., Watson Pharma, Inc. (n/k/a Actavis Pharma, Inc.), and Actavis, Inc. (f/k/a Watson Pharmaceuticals, Inc.)

2. The name of the real party in interest (if the party named in the caption is not the real party in interest) represented by us is:

N/A. The real parties in interest are the same as the parties represented.

3. All parent corporations and any publicly held companies that own 10% or more of the stock of any party represented by us are:

Actavis plc is a publicly held company that owns 10% or more of the stock of Watson Laboratories, Inc., Watson Pharma, Inc. (n/k/a Actavis Pharma, Inc.), and Actavis, Inc. (f/k/a Watson Pharmaceuticals, Inc.). Actavis plc does not have a corporate parent, and no publicly held company owns 10% or more of Actavis plc's stock.

4. The names of all law firms and the partners or associates that appeared for the parties now represented by us in the trial court or expected to appear in this Court are:

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Dated: NOVEMBER 24, 2014

/s/ Steffen N. Johnson
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STATEMENT OF RELATED CASES

Whether the two patents at issue here are infringed by another defendant's products is the subject of a consolidated appeal and companion case, *Novartis Pharms. Corp. v. Par Pharm. Inc.*, Nos. 15-1061, 15-1062 (Fed. Cir.).

The Patent Trial and Appeal Board has instituted *inter partes* review of the same two patents, having found a "reasonable likelihood" that they are invalid for obviousness. *Noven Pharms., Inc. v. Novartis AG*, Nos. IPR2014-00549 & IPR2014-00550 (P.T.A.B. Oct. 14, 2014) (Paper 10); 35 U.S.C. § 314(a); 37 C.F.R. § 42.108(c).

JURISDICTIONAL STATEMENT

This appeal arises from consolidated patent cases brought by Plaintiffs-Appellees ("Novartis") in the District of Delaware. The district court had jurisdiction under 28 U.S.C. §§ 1331 and 1338, and entered judgment on August 4, 2014. A1-4. Defendants-Appellants ("Watson") timely noticed this appeal on September 3, 2014. A62, A72. The district court's judgment is a final adjudication of all claims. This Court has jurisdiction under 28 U.S.C. § 1295(a)(1).

INTRODUCTION

This appeal turns on whether it was obvious to combine a known drug with any known antioxidant. The district court upheld that combination as a patentable "invention," even though the prior art expressly disclosed it. The district court discounted that express disclosure by finding—through implausible interpretations of straightforward text—that the art did not explicitly teach that the combination was actually "needed" or "require[d]." A38, A40. But there is no such legal requirement. Under the district court's heightened legal standard, *any* combination of known elements would be patentable absent an express instruction in the prior art that they *must* be combined. That is not and cannot be the law. The disclosure of the claimed combination itself, regardless of whether it was "needed" or "required," is legally sufficient to establish obviousness. The district court thus legally erred and, in so doing, upheld a claimed combination that all agree would be identified—indeed *was* identified—simply by following completely conventional steps in drug formulation. That is the epitome of obviousness.

The "inventors" of the asserted patents simply took an existing formulation of a known drug, "rivastigmine," and added an extra ingredient called an "antioxidant," which is an "agent that reduces oxidative degradation" of compounds, and was considered a "pharmaceutical necessit[y]" as of the 1998 priority date. A1923. No one disputes that both elements were in the prior art. Nor is there any

dispute that every other detail of the claimed formulation was discussed in a *single* patent application. As the district court confirmed, "[t]he only limitation" of the asserted patents "not disclosed" in that prior art application "is the addition of an antioxidant." A35.

The "inventors" here decided to add an antioxidant to rivastigmine after conducting routine "stability" tests, which determine how fast a drug degrades over time. A3052-57, A1533. The results of those stability tests showed—as they would have shown *anyone* conducting the kind of routine stability testing necessary for FDA approval, *see* 21 C.F.R. § 314.50(d)(1)(i) (1998)—that the drug is susceptible to oxidative degradation. To solve that problem, the inventors added a standard amount of a well-known antioxidant. A3075, A3078-79. That is the full story of how the claimed "invention" came about.

The only disputed question is whether a person of ordinary skill in the art—here, a skilled formulator—would have done the same thing. As the district court acknowledged: "If the answer is yes, the asserted claims … are invalid because the addition of an antioxidant to a pharmaceutical composition that oxidatively degrades is one of several known, obvious solutions." A46.

Clear and convincing evidence shows that the answer to that question is, in fact, "yes." Even *before* conducting routine stability tests, a skilled formulator would have known to combine rivastigmine and an antioxidant, because that exact

combination was disclosed in two prior art references, each of which is independently sufficient to invalidate Novartis's patents. Together, their force is overwhelming—a conclusion buttressed by the Patent Trial and Appeal Board's recent conclusion that there is a "reasonable likelihood" that the claimed invention "would have been obvious" to one of skill in the art. *Noven Pharms.*, Nos. IPR2014-00549 (Paper 10, at 13-14) & IPR2014-00550 (Paper 10, at 15-16).

The '807 patent. The first reference is U.S. Patent No. 4,948,807, which states plainly that "antioxidants … can be incorporated" into formulations including rivastigmine "as required." A1539 (7:48-50). And the patent even specified two "[p]referred antioxidants for use with the compounds of the present invention"—compounds that include rivastigmine. A1539 (7:51-53). Thus, based on the prior art '807 patent, the combination of rivastigmine and an antioxidant was not only obvious—it was *known*.

To the district court, however, that was not enough. It acknowledged that "the '807 patent does disclose the addition of an antioxidant" to rivastigmine, and that "[a]t first glance, this statement appears to support the proposition for which Watson cited it: namely, that it teaches" that rivastigmine "is susceptible to oxidative degradation and needs an antioxidant to maintain stability." A40. Nonetheless, it found that a skilled formulator "would not have been motivated to include an antioxidant in any formulation unless there was evidence of oxidative degrada-

tion," and that the '807 patent's disclosure "does not teach" that rivastigmine "oxidatively degrades" or otherwise "requires an antioxidant." A39-40.

That was legal error. As the Supreme Court confirmed in *KSR International Co. v. Teleflex, Inc.*, a court seeking "to identify a reason … to combine" known elements "cannot be confined by" the prior art's "precise teachings" or "explicit content." 550 U.S. 398, 418 (2007). Rather, it must "take account of the inferences and creative steps that a person of ordinary skill in the art would employ." *Id.* Likewise, "[f]ar from requiring evidence of an explicit motivation to combine," this Court has made clear that "an *implicit* motivation" is enough. *DyStar Textilfarben GmbH v. C.H. Patrick Co.*, 464 F.3d 1356, 1366 (Fed. Cir. 2006). In fact, this Court has "repeatedly held" that a combination may be obvious "even absent any hint of suggestion in the [prior art] references themselves." *Id.* at 1368. A court that requires the prior art "clearly and unequivocally [to] disclose" a "motivation to combine" therefore "err[s] by taking an overly cramped view of what the prior art teaches." *Allergan, Inc. v. Apotex Inc.*, 754 F.3d 952, 963 (Fed. Cir. 2014).

Here, at a bare minimum, the '807 patent would implicitly motivate a skilled formulator to combine rivastigmine with an antioxidant. The patent not only teaches that "antioxidants … *can be* incorporated"—it states that this may be "*required*" and discloses "[p]referred antioxidants *for use with*" rivastigmine. A1539

(7:48-53) (emphasis added). If the '807 patent "does not explicitly disclose a … problem" with oxidation, that is not material. *Sci. Plastic Prods., Inc. v. Biotage AB*, 766 F.3d 1355, 1361 (Fed. Cir. 2014). "[B]y providing for the presence" of an antioxidant in a formulation of rivastigmine, the '807 patent "implicitly acknowledges that there is a potential [oxidation] issue." *Id.* (quotation omitted). And why would a patent identify "antioxidants" that are "[p]referred … for use with" a drug (A1539), if not because that drug is at least "susceptible to oxidative degradation" (A40)? Preventing such degradation is the whole point of adding an antioxidant.

The Elmalem reference. But even assuming, contrary to *KSR*, that obviousness requires an even more explicit motivation to combine, another prior art reference provided it. That reference is a journal article by two of the '807 patent's inventors and a third researcher, Dr. Esther Elmalem, who conducted an experiment comparing four different compounds (including rivastigmine), where "[a]ll drugs were made up freshly in sterile saline, which included an equal weight of" antioxidant "to prevent oxidation." A1876. Thus, Elmalem does not simply disclose that the two were combined. It expressly teaches *why*: use an antioxidant to "prevent oxidation" of rivastigmine *Id*.

For the district court, this still was not enough. Even though Elmalem says an antioxidant was added "to prevent oxidation" of "[*a*]*ll* drugs" in the experiment (*id.* (emphasis added)), the district court announced that it was added only "to pre-

vent oxidation" of a *single*, different drug (A42-43). Without *any* supporting evidence, the court assumed that an antioxidant was added for an unrelated and unstated reason: "to reduce variability" between the tested formulations. A43. But as the court itself recognized, this "interpretation" of Elmalem leads to absurd results: One passage in the article would "not make sense," and the entire experiment it describes "would not be reproducible." A43-44. The court explicitly acknowledged these "criticisms," but clung to its flawed interpretation anyway—without even "attempting to explain scientifically why." A44. That was error.

The district court offered just one concrete justification for its narrow reading of the '807 patent and the Elmalem article—its finding that, as a general matter, antioxidants and drugs are sometimes "incompatible" in a way that "cannot be predicted." A39. But the fact that combining antioxidants with drugs "is *generally* an unpredictable endeavor" "does not matter." *Allergan*, 754 F.3d at 965. The relevant "question is more narrowly whether the success of using" an antioxidant was "reasonably []predictable" with *rivastigmine*. *Id*. And the district court's own findings provide the answer: Both the '807 patent and Elmalem "certainly disclose that an antioxidant *can* be added." A38. Given the prior art's *specific* teachings about rivastigmine, the district court's finding about the *general* "risk of incompatibility" when adding antioxidants to drugs was legally irrelevant.

In the end, the district court was distracted by focusing on whether it was definitively "known" that rivastigmine was subject to oxidation. It *was* "known," because the prior art disclosed that fact. But even if it was not, that could not possibly justify the issuance of a patent. Testing for drug stability issues is not only routine, but actually required for FDA approval. A problem readily identified in the ordinary course using routine skill, followed by an exceedingly routine solution, does not support a patent's validity under either *KSR* or common sense.

The decision below should be reversed, and the asserted patents held invalid as obvious.

STATEMENT OF THE ISSUES

Whether it was obvious to combine a known drug with any known antioxidant where either or both of the following are true: (A) a prior art patent taught that "antioxidants … can be incorporated" with the drug, including "[p]referred antioxidants for use with" the drug (A1539 (7:48-53)); (B) a prior art journal article taught that the drug could be, and was, combined with an antioxidant "to prevent oxidation" (A1876).

STATEMENT OF THE CASE

This appeal concerns the validity of U.S. Patents No. 6,335,031 and No. 6,316,023. A7. Novartis listed both patents in FDA's "Orange Book" as patents covering its rivastigmine transdermal patch, which it sells under the brand name

Exelon®. *Id.* After Watson sought FDA approval to market generic versions of Exelon®, Novartis sued Watson for infringement. A8.

Following a bench trial, the district court held that Watson's proposed generic products infringe the asserted claims of Novartis's patents, and that those claims are not invalid as obvious. *Novartis Pharms. Corp. v. Par Pharm., Inc.*, 2014 WL 2798703 (D. Del. June 18, 2014); A5-47. Watson appealed.

STATEMENT OF FACTS

A. Novartis's patents claim the combination of a transdermal formulation of rivastigmine with an antioxidant.

1. Novartis asserted seven claims of the '031 and '023 patents against Watson. Those claims are generally directed to the combination of a transdermal formulation of rivastigmine and an antioxidant. The district court divided them into two groups: the "presence" claims and the "function" claims. A9-11. The term "antioxidant" is a limitation of each asserted claim.

Claims 3 and 7 of the '031 patent, and claims 2 and 7 of the '023 patent, are the "presence" claims. They cover pharmaceutical compositions or transdermal devices "comprising" rivastigmine and an "antioxidant." *Id.*; A736, A744. Claims 13, 16, and 18 of the '031 patent, which cover pharmaceutical compositions or a method of stabilizing such compositions, are the "function" claims. They "have an additional requirement that the antioxidant interact with [rivastigmine] to reduce degradation." A11, A737. Adopting Novartis's proposed construction of the term

"antioxidant," the district court defined that term broadly as any "agent that reduces oxidative degradation." A11, A139.

2. Another limitation of each asserted claim is rivastigmine, which Novartis's patents refer to by either its chemical name or "Compound A." A736-37, A744. Rivastigmine is the active ingredient in Novartis's Exelon® patch product. *Id.* By inhibiting the breakdown of an enzyme in the brain called acetylcholinesterase, or "AChE," rivastigmine helps to treat Alzheimer's disease. A7.

Rivastigmine is the S-enantiomer of a racemic compound called RA7. A9. A "racemic" compound is a mixture of two "enantiomers"—one "R" and one "S"—which "are identical in all respects except for the fact that they are mirror images of each other." A9 n.3. *See Aventis Pharma Deutschland GmbH v. Lupin, Ltd.*, 499 F.3d 1293, 1301 (Fed. Cir. 2007). Thus, RA7 is a mixture of 50% R-enantiomers and 50% S-enantiomers (i.e., rivastigmine). A2881.

At trial, Novartis attempted to minimize the relevance of prior art that discusses RA7 (instead of rivastigmine in isolation) by arguing that "a racemate and its constituent enantiomers are chemically distinct compounds." A3392. But both the district court and Novartis's own expert recognized that any distinction between RA7 and rivastigmine does not matter. As Novartis's expert explained, the "stability toward oxidative degradation of rivastigmine[] and RA7 is the same, and it's not a controversial issue." A37 n.17, A3174.

In any event, although Novartis's patents require rivastigmine, they do not exclude its corresponding R-enantiomer or otherwise require that it be separated from the racemic mixture. In setting forth the required claim elements, all of the claims use the word "comprising"—"a term of art used in claim language which means that the named elements are essential, but other elements may be added and still form a construct within the scope of the claim." *Genentech, Inc. v. Chiron Corp.*, 112 F.3d 495, 501 (Fed. Cir. 1997); A2901.

The prosecution history of Novartis's patents confirms that they do not exclude the R-enantiomer, which is also called the "(R) isomer." During prosecution, the examiner initially rejected the claims for not being enabled because he believed rivastigmine "must be substantially free of its (R) isomers to be used in the proposed treatment" of Alzheimer's disease. A809-10. But rather than amend the claims to limit them to pure rivastigmine, Novartis argued that "the (R) isomers" are not "in any way detrimental to the proposed treatments," and thus that "it is not necessary that the pharmaceutical composition be substantially free of the (R) isomer." A827. The examiner accepted this argument and allowed the unbounded claims. A836. As a result, because RA7 contains rivastigmine, the asserted claims cover the combination of an antioxidant with RA7. A2906-07.

B. The claimed transdermal formulation of rivastigmine was known.

1. Novartis's patents are not the first to claim rivastigmine itself. Nor are they the first to claim the pharmaceutical formulation of rivastigmine in a transdermal patch. As the patents acknowledge, "a pharmaceutical composition" of rivastigmine for "transdermal administration" that is useful in "the treatment of Alzheimer's disease" was earlier "disclosed in published UK patent application GB 2 203 040" ("GB '040"). A733 (1:6-16), A741 (1:7-17).

GB '040 describes virtually every aspect of the claimed invention. It describes rivatigmine's ability for "marked and selective inhibition" of AChE, which is the mechanism of action that makes it "useful for the treatment of … Alzheimer's." A1545, A1552, A38. And it explains that rivastigmine "reach[es] the central nervous system rapidly," "exert[s] a brain region-selective inhibition of [AChE]," has a "long duration of action," and is "well-tolerated." A1546, A1552.

GB '040 also explains that the "transdermal administration" of rivastigmine —which improves "tolerability" by providing a "slow onset of action" and "induces a long-lasting and constant inhibition" of AChE—is "particularly advantageous." A1556, A38. Moreover, GB '040 notes that rivastigmine has "good skin penetration" and therefore "may require a relatively low quantity in the transdermal composition when compared with the oral daily dose." A1556, A1560.

2. Like Novartis's patents here, GB '040 discusses both the free base and the acid addition salt forms of rivastigmine, which "may be prepared from the racemate [i.e., RA7] by separation of the enantiomers in accordance with known methods." A1545, A38, A736 (cl. 1), A744 (cl. 1). Example 2 of GB '040 also discloses a transdermal patch with a backing film to support a pharmaceutical composition of rivastigmine—the same design as the Exelon® patch. A1562, A7-8. Further, like Novartis's patents, GB '040 discloses "a pharmaceutical carrier or diluent suitable for systemic transdermal administration." A1559, A38. Finally, GB '040 discloses "a therapeutically effective dose" of rivastigmine (A1559-60), which "falls within the range of the asserted claims" (A38, A2884-85).

It is thus undisputed that "[t]he only limitation of the '023 and '031 patents' asserted claims not disclosed by GB '040 is the addition of an antioxidant." A35.

C. The claimed antioxidants, and their use in transdermal formulations, were well known in the prior art.

1. As its name suggests, "an antioxidant is a substance capable of inhibiting oxidation." A1923. By 1998, when the applications that led to Novartis's patents were filed, it was well known that "[o]xidation is a prime cause of product instability"—a problem "well-defined by pharmaceutical scientists." A1925-26. In fact, for "pharmaceutical products subject to deterioration by oxidative processes," antioxidants were "pharmaceutical necessities." A1923.

More specifically, Novartis's claimed antioxidants—the only limitation of its patents not disclosed by GB '040—were well known. As the district court confirmed, the prior art's *Handbook of Pharmaceutical Excipients* "discloses the antioxidants claimed in the patents in suit, in amounts that fall within the claimed concentration ranges." A45, A2036-65, A2907-23. Moreover, it is undisputed that determining the amount of antioxidant to use in a given pharmaceutical formulation was a matter of only routine skill and "standard testing." A2980-81.

Nor was there anything inventive about incorporating these antioxidants into a transdermal patch. As the district court found, an earlier U.S. patent, No. 5,580,572, "teaches the inclusion of an antioxidant, within the concentration ranges claimed in the patents in suit, to stabilize" a "transdermal matrix system" like the one claimed in Novartis's patents. A45, A1680 (4:47-52), A1686 (16:23).

2. Although "routine testing" is necessary to determine a drug's chemical stability—and thus whether it may need an antioxidant—that testing has long been required by the FDA. A2975; *see* 21 C.F.R. § 314.50(d)(1)(i) (1998). In 1994 —years before Novartis's patents were filed—the FDA published guidelines "useful to applicants submitting new drug applications" that "reflect formal scientific principles for stability testing," and "exemplify the core stability data package appropriate for new drug[s]." A1521, A1523.

Among other procedures, the FDA's guidelines describe routine tests to "establish the inherent stability" of a drug and its "degradation pathways," including "the effect of … oxidation." A1533. As Watson's expert explained in unrebutted trial testimony, the tests described in the FDA's guidelines can determine "whether or not a particular composition require[s] an antioxidant." A2978-79.

3. In fact, Novartis's decision to add an antioxidant to its claimed formulation resulted from those very same tests. As one of the named inventors testified, he and his team first detected "degradation compounds showing up in the transdermal system" that they were designing "in June of 1995"—after just "three months" of "stability studies." A3052, A3075. The team acted quickly "to identify the structure of the degradation products" and was soon "confident it was an oxidative reaction." A3055, A3059.

By "July of 1995"—less than a month after discovering the stability problem—the inventor "wrote [a] memo" suggesting "the addition of an antioxidant" (A3075), which he characterized as "a minor modification" to the formulation (A3057). Indeed, to formulate a stable rivastigmine product, all he had to do was "experiment[] with two antioxidants," which conveniently "had already been used" in other, previously "approved drug products." A3078-79.

D. The addition of antioxidants to rivastigmine for the purpose of preventing oxidative degradation was known.

As discussed, the prior art discloses both elements of Novartis's patents: the same transdermal formulation of rivastigmine, and the same antioxidants. But it teaches more than that. It also discloses the combination of these elements. In fact, even without the benefit of stability tests that are both routine and mandatory, each of two prior art references would make it obvious for a person of ordinary skill in the art—a "POSA"—with a reasonable expectation of success, to combine rivastigmine with an antioxidant.

1. The '807 patent teaches that "antioxidants … can be incorporated as required" with rivastigmine, and discloses "[p]referred antioxidants for use with" rivastigmine.

The '807 patent is directed to "novel phenyl carbamates"—a class of compounds that includes rivastigmine—for use in "pharmaceutical compositions" that have "anticholinesterase activity" and are therefore "useful for the treatment of … Alzheimer's disease." A1536 (1:9-12), A1542 (13:1-5). The '807 patent specifically directs a POSA to RA7 (which, as discussed, is 50% rivastigmine). RA7 is one of only eight "[p]referred compounds," and one of only three compounds that the patent actually claims. A1538 (5:40-50), A1542 (cl. 3), A2889-90, A40.

The '807 patent also teaches the combination of RA7 with an antioxidant. A2891-94, A2877. It first generally explains that the "compounds of the invention" can be "utilized by formulating … them in compositions," which in turn may

include various inactive ingredients—including those acting as a "stabilizer"—"as called for by accepted pharmaceutical practice." A1539 (7:15-24). The '807 patent then specifically explains that "antioxidants … can be incorporated as required." A1539 (7:48-50). In fact, it names "sodium metabisulphite and ascorbic acid" as the "[p]referred antioxidants for use with the compounds of the present invention." A1539 (7:51-53). The latter antioxidant, ascorbic acid, is also claimed in Novartis's patents here. A737 (cls. 13, 16), A744 (cl. 2).

2. The Elmalem article teaches the combination of rivastigmine with an antioxidant "to prevent oxidation."

Independently, a published journal article in the prior art by Dr. Elmalem and two of the '807 patent's inventors likewise teaches the combination of RA7—and thus of its S-enantiomer, rivastigmine—with an antioxidant. The Elmalem article describes a study comparing the effects, on rabbits, of an older AChE inhibitor called "physositgmine" with the three compounds claimed in the '807 patent. A1875. The study also compared the degree to which each compound inhibited AChE in three areas of the rabbits' brains. A1876-80.

Under a subheading labeled "Drugs" in the "Methods" section of the article, it lists "[t]he agents tested" as RA6, RA7, RA16, and physostigmine. A1876. It then explains: "All drugs were made up freshly in sterile saline, which included an equal weight of sodium metabisulphite, to prevent oxidation." *Id.* As noted above, the '807 patent lists "sodium metabisulphite" as one of the "[p]referred antioxi-

dants for use with" RA7. A1539 (7:51-53). Elmalem's instruction to a POSA is thus explicit: When formulating rivastigmine, make sure to add an antioxidant—"to prevent oxidation." A1876, A2931, A2950.

E. The district court upheld Novartis's patents solely because it found that a person of ordinary skill in the art would not have been motivated to combine rivastigmine with an antioxidant.

At trial, it was undisputed that "[t]he use of rivastigmine in a transdermal patch to treat Alzheimer's disease was known." A37. It was also undisputed that the use of "the antioxidants claimed," "in amounts that fall within the claimed concentration ranges," was known. A45.

The trial court thus found that "the obviousness determination in this case turns" on whether a POSA "would have known rivastigmine was susceptible to oxidative degradation." A46. "If the answer is yes," the court recognized, "the asserted claims of the '023 and '031 patents are invalid because the addition of an antioxidant to a pharmaceutical composition that oxidatively degrades is one of several known, obvious solutions," which would have been "'predictable'" and "'within [a POSA's] technical grasp.'" *Id.* (quoting *KSR*, 550 U.S. at 421).

Supported by "highly qualified" expert testimony (A44), Watson showed that the answer to that question is "yes," because both the '807 patent and Elmalem teach that RA7—and thus rivastigmine—should be combined with an antioxidant to prevent oxidative degradation (A2877, A2931, A2950). But despite Watson's

"logical" argument, the district court decided that neither reference provides "a motivation to add an antioxidant to … rivastigmine." A38.

1. The court first considered the '807 patent's teaching that "antioxidants … can be incorporated" with RA7, including "preferred antioxidants." A40, A1539 (7:48-50). The court admitted that "this statement appears to support the proposition that RA7 is susceptible to oxidative degradation and needs an antioxidant to maintain stability." *Id.* Nevertheless, while acknowledging that "the '807 patent disclose[s] the addition of an antioxidant 'as required,'" the court concluded that "nothing in the '807 patent suggests RA7 requires an antioxidant." *Id.*

In reaching that conclusion, the district court expressly relied on the lack of details in the '807 patent about exactly how or when to add an antioxidant. In particular, the court noted that "there is no specific example in the '807 patent combining RA7 with an antioxidant"; "no discussion of the appropriate amount of antioxidant"; and "no mention of any observed oxidative degradation" or "stability data." A40-41. The court also believed that the '807 patent teaches *away* from adding an antioxidant—notwithstanding its disclosure of "[p]referred antioxidants for use with" RA7—because it also says that RA7 "show[s] greater chemical stability" (but not greater *oxidative* stability) "than physostigmine." A41.

2. Next, the court turned to the statement in Elmalem that "[a]ll drugs" in the authors' experiment, including RA7, "were made up freshly in sterile saline,

which included an equal weight of sodium metabisulphite"—a well-known antioxidant that the '807 patent identifies as one of two "preferred antioxidants" (A1539 (7:51-53))—"to prevent oxidation." A41-42, A1876. Despite Elmalem's plain statement that an antioxidant was added "'to prevent oxidation'" of "'[*a*]*ll* drugs,'" the court favored Novartis's "decisively divergent" interpretation that the authors added an antioxidant "to prevent oxidation" of only *one* drug—physostigmine. A42-43 (emphasis added).

According to this "interpretation," the authors added an antioxidant to RA7 *not* because they were concerned about preventing its oxidation (as they said), but because there otherwise "would be no way to determine whether any observed difference" in the test "was attributable to the relative chemical activity of the drug or to the presence of the antioxidant." A42. In support of this view, however, the court cited *no* evidence that an antioxidant plausibly could have affected any "observed difference" in the experiment. As Novartis's expert admitted, "[no]thing in th[e] publication … indicates that Dr. Elmalem or her colleagues thought that sodium metabisulphite would have an effect" on their test results. A3213.

In any event, if "reduc[ing] one of the variables in the experiment" were truly the reason for adding the antioxidant to RA7, all agreed that it would also need to be added to "the saline placebo." A42-43. But as Watson pointed out—and the court seemingly acknowledged—this leads to two incongruous results:

First, Elmalem says that an antioxidant was added only to "drugs"—not to saline, which "is not mentioned as a drug in the 'Drugs' section of the paper." A43. As the district court recognized, moreover, "it does not make sense that '[a]ll drugs were made up freshly in sterile saline' if the authors considered saline itself to be a drug." *Id*. Nevertheless, the court "accept[ed] Novartis's argument" that "the study's use of the word 'drugs' includes … saline acting as a placebo," based solely on the following sentence in "[t]he article summary: 'Each drug, RA6, (1 mg i.v., 2 mg s.c.) RA7 (1 or 2 mg i.v.); RA15 (0.25 or 0.5 mg i.v.), physostigmine (0.05 or 0.1 mg i.v.) *or saline* (1 ml), was injected simultaneously with morphine (8 mg i.v.) to groups of 6-10 rabbits.'" A43, A1875 (emphasis added).

Second, the district court acknowledged that if an antioxidant were added to saline, "the methodology of Elmalem would not be reproducible." A44. As Watson's expert explained, Elmalem discloses that a specific concentration of each drug was prepared in saline along with "an equal weight" of antioxidant, which tells a POSA "to add an amount of antioxidant to each drug formulation that is equivalent to the weight of the drug in that solution." *Id.*; A2943. By contrast, adding "an equal weight" of antioxidant to the plain saline solution is meaningless: A POSA "would not know how much antioxidant to add." A44.

The district court acknowledged these "criticisms" but accepted Novartis's interpretation of Elmalem anyway. *Id*. The court justified its conclusion solely

based on what it called the bare "credibility" of the parties' experts. *Id*. It expressly declined "to attempt[] to explain scientifically" the basis for its holding. *Id*.

3. Undergirding the district court's narrow reading of the '807 patent and Elmalem was its view that the prior art as a whole would have discouraged a POSA from adding antioxidants to drugs in general. The court reasoned that inactive ingredients (or "excipients") "offer no therapeutic benefit" and "can be incompatible with the drug or other excipients in the pharmaceutical composition, which could lead to a deleterious effect on the drug's performance." A39. "The compatibility of an excipient with a given pharmaceutical composition," the court stated, typically "cannot be predicted without experimentation." *Id.*

The court further explained that "oxidative degradation is not the only degradation pathway; there were many known types of degradation at the time of the invention." *Id*. "[D]ue to the risk of incompatibility" between pharmaceutical ingredients, the court found that "a P[OSA] would not have added an excipient to prevent each … type[] of degradation." *Id*. The court thus concluded that a POSA, fearing such an "incompatibility," would not have added an antioxidant to rivastigmine "unless there was evidence of oxidative degradation" to prove that its "use cannot be avoided." *Id.* (quotation omitted).

In reaching that conclusion, the district court did not mention that "evidence of oxidative degradation" would inevitably have been unearthed in mandatory sta-

bility tests. *Supra* at 14-15. The court also ignored its own factual finding that both the '807 patent and Elmalem "certainly disclose that an antioxidant *can* be added to RA7"—and therefore to rivastigmine. A38. Nor did the court discuss the disclosures in these references that rivastigmine, when formulated with an antioxidant, remains effective for treating Alzheimer's disease. *Infra* at 56-57.

F. The Patent Trial and Appeal Board found a "reasonable likelihood" that Novartis's patents are invalid.

In contrast to the decision below, the Patent Trial and Appeal Board ("PTAB") was recently "persuaded," based on petitions for *inter partes* review filed by another party, that there is a "reasonable likelihood … that it would have been obvious" at the time that Novartis's patents were filed "to combine an antioxidant with the pharmaceutical composition disclosed by Enz [i.e., GB '040]." *Noven Pharms.*, No. IPR2014-00549 (Paper 10, at 13-14).[1]

In particular, the PTAB found that "Rosin [i.e., the '807 patent] and Elmalem [each] suggest[] [that] combining an antioxidant with the racemate, RA7, may be useful." *Id*. at 14. "Elmalem discloses adding an antioxidant to prevent oxidation of various compounds, including RA7," the PTAB explained, and a POSA

[1] As noted above (at 1), the PTAB has instituted *inter partes* review of *both* patents asserted here. For simplicity, we cite only the PTAB's decision regarding the '023 patent (No. IPR2014-00549 (Paper 10)). However, the PTAB made identical findings regarding the '031 patent (*see* No. IPR2014-00550 (Paper 10)).

"would have considered the prior art teaching and/or suggestion to add an antioxidant to RA7 to be applicable also to its S-enantiomer, rivastigmine." *Id*.

Although the PTAB has not yet "made a final determination on the patentability of any challenged claim," it confirmed that there was "sound reasoning with [a] rational underpinning to support a motivation for combining the teachings of the prior art." *Id.* at 26, 14. Specifically, based on the record before it to date, the PTAB concluded that combining rivastigmine with an antioxidant "would have amounted to combining a familiar element according to a known method to yield no more than a predictable result." *Id.* at 17 (citing *KSR*, 550 U.S. at 416).

SUMMARY OF ARGUMENT

The prior art disclosed every element of Novartis's patents. The drug rivastigmine was well known, as was its use in transdermal formulations to treat Alzheimer's disease. The antioxidants claimed in Novartis's patents, and their use in the same amounts in transdermal devices, were also well known. Thus, the only question is: Would a POSA have been motivated to combine these known elements with a reasonable expectation of success? And two pieces of prior art each definitively show that the answer is "yes."

A. First, the '807 patent unambiguously teaches the combination of rivastigmine with an antioxidant. Indeed, it not only discloses that "antioxidants … can be incorporated as required" into pharmaceutical compositions of rivastigmine,

it specifically discloses two "[p]referred antioxidants for use with" the drug. A1539 (7:48-53). Yet the district court concluded that the '807 patent would not have motivated a POSA to combine rivastigmine with an antioxidant. That holding was founded on multiple legal errors.

1. While acknowledging that the '807 patent "disclose[s] the addition of an antioxidant" to rivastigmine "as required," the court held that it "does not teach" the fact that rivastigmine "oxidatively degrades" and thus "requires an antioxidant." A40. But under the correct legal standard, that kind of explicit teaching is unnecessary. As *KSR* confirms, "obviousness analysis" cannot "be confined by" the "explicit content of issued patents," but instead must "take account of the inferences and creative steps that a person of ordinary skill in the art would employ." 550 U.S. at 418. Likewise, this Court has "repeatedly held that an implicit motivation to combine" known elements "*requires*[] consideration of common … sense," and can be shown "even absent any hint of suggestion in the references themselves." *DyStar*, 464 F.3d at 1367-68.

When *KSR* and this Court's precedent are properly applied, the fact that the '807 patent "does not explicitly disclose [an oxidation] problem" in so many words is immaterial. *Sci. Plastic Prods.*, 766 F.3d at 1361. "[B]y providing for the presence of an [antioxidant]" in a pharmaceutical composition, the '807 patent at least "implicitly acknowledges that there is a potential [oxidation] issue" with rivastig-

mine (*id.*)—and thus would have motivated a POSA to combine it with an antioxidant. Indeed, the term "antioxidant" itself suggests the need to combat oxidation.

2. In holding otherwise, the district court erroneously relied on the absence of details in the '807 patent about how or when exactly to add an antioxidant. As this Court has made clear, however, such "silence does not imply teaching away" and does not disturb "[a] motivation to combine [that] may be implicit" (*Allergan*, 754 F.3d at 964)—especially where, as here, the relevant details are "disclosed elsewhere in the prior art" (*In re Haase*, 542 F. App'x 962, 967 (Fed. Cir. 2013)).

Indeed, it is undisputed that other prior art references disclose the *same* antioxidants as Novartis's patents, in the *same* amounts, and even their use in the *same* "transdermal" type of formulation. *Supra* at 14. By requiring the '807 patent—a single reference—to reiterate details that a POSA already would have known, the district court "confused obviousness with anticipation," which of course requires that all claim elements be disclosed within a *single* reference. *SIBIA Neurosciences, Inc. v. Cadus Pharm. Corp.*, 225 F.3d 1349, 1357 (Fed. Cir. 2000).

3. Furthermore, despite the '807 patent's case-dispositive disclosure of "[p]referred antioxidants for use with" rivastigmine, the district court found that the patent would not have motivated a POSA to use antioxidants because it "portrays" the chemical "stability" of rivastigmine "in a positive light." A41. But under settled law, the fact that the '807 patent "specifically discloses a preference"

for antioxidants conclusively establishes that it "does not teach away from using" them. *In re Chapman*, 595 F.3d 1330, 1337-38 (Fed. Cir. 2010).

Even putting that aside, the district court's reading of the '807 patent is untenable. The patent merely says that RA7—the racemic compound that contains rivastigmine—has "greater chemical stability than" an older compound that Novartis's expert agreed is highly *un*stable. A41, A3261. But the patent does *not* say that rivastigmine *is* stable, much less that it is stable against *oxidation*. In fact, undisputed evidence shows that the statements that the district court relied on are about a *different* type of stability—called "hydrolysis"—which "[a]n antioxidant will not reduce." A3156. When it comes to oxidation, however, a POSA would have expected rivastigmine to degrade, and thus would have been motivated to combine it with an antioxidant. *Infra* at 44-46.

B.1. Even apart from the '807 patent, the Elmalem article independently would have taught a POSA to combine rivastigmine with an antioxidant. Elmalem describes an experiment comparing four drugs, including the racemate that is 50% rivastgimine. A section of the article entitled "Methods" explains that "[a]ll drugs were made up freshly in sterile saline, which included an equal weight of [antioxidant] to prevent oxidation." A1876. That should have ended the matter: Even if obviousness required an explicit motivation to combine (and it does not), Elma-

lem's teaching that rivastigmine was combined with an antioxidant "to prevent oxidation" would amply supply it.

Yet the district court did not see it that way. With no basis in the article's text, it adopted Novartis's "decisively divergent" "interpretation" that the authors added the antioxidant only to protect one of the *other* drugs, and then added it to rivastigmine merely "to reduce variability." A42-43. That reading of the prior art was clearly erroneous.

2. If an antioxidant were actually needed "to reduce variability" between the drug compositions, all agree that it would also be needed for the saline placebo. *Id.* But Elmalem says the antioxidant was added only to "drugs," and saline—which is just "table salt in water"—is "not a drug." A3164, A2945. To conclude otherwise, the district court had to misread a single sentence in the article's *abstract* to mean that the authors defined "drug" to include "saline," when multiple passages in the article's actual *body* distinguish sharply between saline and drugs, confirming that the authors did not depart from its ordinary meaning. *Infra* at 51.

3. The district court's reading of Elmalem is also incorrect because it renders the experiment impossible to reproduce. Although the article discloses the amount of antioxidant that was added to each actual drug—an "equal weight" to the drug's concentration—it says nothing about adding an antioxidant to the saline placebo, let alone how *much* antioxidant to add. A1876, A2944-45. To get around

that problem below, Novartis argued that the phrase "equal weight" refers to some undisclosed "weight" that happens to be "equal" for every formulation. But when asked whether he could calculate how much antioxidant to add under that interpretation to "any of the[] solutions," Novartis's expert replied: "No, I don't know." A3211. By contrast, under Watson's text-based interpretation, he admitted that "[o]ne would be able to calculate it." A3212.

That too should have been the end of the matter. "[B]iological tests generally demand" methodologies that "ensure … reproducible results." *Embrex, Inc. v. Serv. Eng'g Corp.*, 216 F.3d 1343, 1348 (Fed. Cir. 2000). As Novartis's expert conceded, "one of the purposes of the methods sections" in publications like Elmalem is "to allow scientific peers to reproduce the work that is described." A3210-11. By adopting an interpretation of Elmalem that obstructs this central purpose of scientific literature, the district court clearly erred.

C. At all times, the district court based its crabbed reading of the prior art—and its strict requirement for explicit "evidence of oxidative degradation"—on a generalized "risk of incompatibility" between drugs and antioxidants that "could lead to a deleterious effect on the drug's performance" and "cannot be predicted without experimentation." A39. But even assuming that such a risk exists with *other* drugs, the only salient question is whether a POSA would have expected antioxidants to be compatible with *rivastigmine*. Under the district court's own fac-

tual findings, the answer is yes: When it comes to that *particular* drug, the prior art "certainly disclose[s] that an antioxidant *can* be added." A38.

But that is not all. Elmalem demonstrates with actual testing data that rivastigmine, when combined with a "well-known antioxidant" (A2938), produces a "dose-related," "maximum inhibition of more than 70%" of AChE in "three regions" of the brain (A1877). Because rivastgimine's inhibition of AChE is the biological mechanism that "makes it useful for the treatment of Alzheimer's disease" (A38), Elmalem would have put to rest any concern that an antioxidant might have a "deleterious effect on the drug's performance" (A39).

Likewise, the '807 patent teaches that "antioxidants … can be incorporated" successfully into pharmaceutical compositions of rivastigmine "for the treatment of Alzheimer's disease." A1539 (7:48-53), A1542 (13:1-5, cl. 4). As with all "claimed and unclaimed disclosures in a prior art patent," the district court was legally required to "presum[e]" that the '807 patent's therapeutic compositions "are enabled." *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1355 (Fed. Cir. 2003). Since the '807 patent taught that combining rivastigmine with an antioxidant would work, the district court's reliance on the general unpredictability of combining ingredients in other drugs had no legal basis.

The decision below should be reversed.

STANDARD OF REVIEW

"The ultimate conclusion of whether a claimed invention would have been obvious is a question of law reviewed de novo." *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1359 (Fed. Cir. 2007). That question is based on "underlying findings of fact," which are "reviewed for clear error." *Id.* "A factual finding is clearly erroneous if, despite some supporting evidence, the reviewing court on the entire evidence is left with the definite and firm conviction that a mistake has been committed." *Id.* (quoting *United States v. U.S. Gypsum Co.*, 333 U.S. 364, 395 (1948)).

Where, as here, "every limitation of the asserted claims" is disclosed in the prior art, the claims are invalid as obvious if "a person of ordinary skill in the art would have been motivated to combine those teachings to derive the claimed subject matter with a reasonable expectation of success." *Bayer Healthcare Pharms., Inc. v. Watson Pharms., Inc.*, 713 F.3d 1369, 1375 (Fed. Cir. 2013). "The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *KSR*, 550 U.S. at 416.

ARGUMENT

Individually and collectively, the '807 patent and the Elmalem reference definitively establish that Novartis's patents are invalid for obviousness.

The sole issue here is whether it was obvious to combine a known drug with any known antioxidant. Because the prior art taught that precise combination, No-

vartis's patents are invalid as obvious. The district court was able to conclude otherwise only by applying incorrect legal standards and making clear factual errors.

As shown in Part A, the district court legally erred in failing to recognize that the '807 patent's disclosure of "[p]referred antioxidants for use with" rivastigmine provides at least an implicit motivation to combine that drug with an antioxidant. As shown in Part B, the court clearly erred by distorting Elmalem's express instruction that rivastigmine should be combined with an antioxidant "to prevent oxidation." And as shown in Part C, the fact that some antioxidants may be incompatible with drugs *other* than rivastigmine—a key premise in the district court's obviousness analysis—is legally irrelevant.

A. The district court's holding that the '807 patent would not have motivated a POSA to combine rivastigmine with an antioxidant was incorrect as a matter of law.

The '807 patent would have motivated a POSA, with a reasonable expectation of success, to combine the known transdermal formulation of rivastigmine disclosed in GB '040 with any of the known antioxidants disclosed in the prior art's *Handbook of Pharmaceutical Excipients*. The result of that straightforward combination is the obvious "invention" claimed in Novartis's patents.

It is undisputed that the '807 patent discloses "the addition of an antioxidant to RA7"—the racemic mixture that is 50% rivastigmine. A40, A37 & n.17; *supra* at 16-17. But the '807 patent does not just teach that "antioxidants … *can* be in-

corporated" with rivastigmine "as required." A1539 (7:48-50) (emphasis added). It also discloses two "[p]referred antioxidants *for use with* the compounds of the present invention," which include rivastigmine. *Id.* at 7:51-53 (emphasis added). As Watson's "highly qualified" expert explained at trial (A44), the '807 patent's disclosures about combining rivastigmine with preferred antioxidants implicitly "teach … that rivastigmine is susceptible to oxidative degradation" (A2877).

The '807 patent therefore renders all asserted claims obvious. Indeed, it "go[es] beyond just illuminating a known problem" of rivastigmine's susceptibility to oxidative degradation—it "also expressly propose[s] the claimed solution" of adding an antioxidant to prevent it. *Watson Pharms.*, 713 F.3d at 1375-76.

The district court nevertheless held that the '807 patent would not have motivated a POSA to combine rivastigmine with an antioxidant. A40. "Although the '807 patent does disclose the addition of an antioxidant," the court declared that "it does not teach" that rivastigmine "oxidatively degrades" or otherwise "requires an antioxidant." *Id*. Reasoning that "[t]here can be no motivation … to solve a problem that no one knows exists"—and ignoring that the very purpose of *anti*oxidants is to prevent the *problem* of oxidation—the court upheld Novartis's patents. A46. But that reasoning does not withstand scrutiny.

1. Contrary to the district court's analysis, an explicit motivation to combine known elements is not required.

a. As the Supreme Court reaffirmed in *KSR*, "when a patent simply arranges old elements with each performing the same function it had been known to perform and yields no more than one would expect from such an arrangement, the combination is obvious." 550 U.S. at 417 (citation omitted). And although it "can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements," a court "need not seek out precise teachings directed to the specific subject matter of the challenged claim." *Id.* at 418.

Nor can a court allow its "obviousness analysis" to "be confined by" an "overemphasis on the … explicit content of issued patents" in the prior art. *Id.* Rather, a court must also "take account of the inferences and creative steps that a person of ordinary skill in the art would employ." *Id*. If those "inferences and creative steps" would lead a POSA to "pursue the known options within" a POSA's "technical grasp," then even a "combination of elements" that is only "'obvious to try'" is "obvious under [35 U.S.C.] § 103." *Id.* at 421.

This Court's precedent is to the same effect: In determining obviousness, "there is no requirement that the prior art contain an express suggestion to combine known elements to achieve the claimed invention." *Motorola, Inc. v. Interdigital Tech. Corp.*, 121 F.3d 1461, 1472 (Fed. Cir. 1997). In fact, "[f]ar from requiring

evidence of an explicit motivation to combine" prior art elements, this Court has repeatedly found combinations of known elements to be obvious based only on an "*implicit* motivation to combine." *DyStar*, 464 F.3d at 1368; *accord Allergan*, 754 F.3d at 963; *Alza Corp. v. Mylan Labs., Inc.*, 464 F.3d 1286, 1291 (Fed. Cir. 2006).

Moreover, the implicit motivation to combine known elements "need not be found in the references sought to be combined, but may be found in … the nature of the problem itself." *DyStar*, 464 F.3d at 1361. "[A] conclusion of obviousness" may arise "from common knowledge and common sense of the person of ordinary skill in the art"—"even absent any hint or suggestion in the references themselves." *Id.* at 1368 (quotation omitted). The obviousness analysis "not only permits, but *requires*" this "consideration of … common sense." *Id.* at 1367.

The district court's decision contravened these precedents. It acknowledged that the '807 patent "certainly disclose[s] that an antioxidant *can* be added" to rivastigmine, yet decided that the patent fails to teach "that rivastigmine is susceptible to oxidative degradation." A40. In reaching that conclusion, the court "err[ed] by taking an overly cramped view of what the prior art teaches." *Allergan*, 754 F.3d at 963. Even assuming that the '807 patent does not "unequivocally disclose" that rivastigmine oxidatively degrades, that "does not diminish … the fact that [the '807 patent] *does* suggest th[at] possibility." *Id.* (quotation omitted).

Indeed, why *else* would the patent suggest that an antioxidant "can be incorporated as required" with rivastigmine—and name "[p]referred antioxidants for use with" it (A1539 (7:48-52))—if not because rivastigmine is at least "*susceptible*" to oxidation (A46 (emphasis added))? It does not take many (if any) "inferences and creative steps" (*KSR*, 550 U.S. at 418) to understand that an "anti*oxidant*" prevents *oxidation*, and that would be especially clear to a POSA—one with "an advanced degree" and "experience developing pharmaceutical formulations" (A35-36). The purpose for "the addition of an antioxidant" has always been to make a product "resistant to oxidation"—that "broad conception … does not involve invention." *In re Dreshfield*, 110 F.2d 235, 239 (C.C.P.A. 1940). Thus, even assuming that the '807 patent does not outright *instruct* a POSA to combine an antioxidant with rivastigmine, it plainly provides "an implicit, indeed common-sensical, motivation" to do so. *DyStar*, 464 F.3d at 1368.

b. The district court's observation that "[t]here can be no motivation … to solve a problem that no one knows exists" (A46), while generally true, is thus irrelevant. In providing a solution to a potential problem, the prior art may implicitly reveal the problem to be solved.

This Court recently confirmed that point in *Scientific Plastic Products*, 766 F.3d 1355. The patents there claimed a resealable cartridge for low pressure liquid chromatography, or "LPLC," which is a method of isolating chemicals. *Id*. at

1356-57. There, as here, a single prior art reference "disclose[d] all of the features" of the claimed invention but one: a "pressure-resistant cap" to prevent the LPLC cartridge from leaking. *Id*. at 1358. There, as here, the missing feature was disclosed by two other references, which related to other types of liquid containers. *Id*. And after an accused infringer sought *inter partes* reexamination, the Patent Office found that it was obvious to combine these known elements to arrive at the claimed invention: an LPLC cartridge combined with a pressure-resistant cap. *Id.*

The patentee appealed, arguing that the prior art "does not explicitly disclose a leakage problem" with LPLC cartridges, and thus that "a person of ordinary skill would not have perceived any need to improve such cartridges" by adding the pressure-resistant cap. *Id.* at 1361. But this Court affirmed. To be sure, no reference expressly warned that LPLC cartridges "leaked." But "by providing for the presence of an O-ring"—a circular gasket commonly used to seal containers—the reference that described the prior art's LPLC cartridge "implicitly acknowledge[d] that there is a potential leakage issue." *Id.* (quotations omitted).

The facts here present an even stronger obviousness case than in *Scientific Plastic Products*. Granted, the '807 patent "does not explicitly disclose [an oxidation] problem" with rivatigmine—at least not in so many words. *Id.* But "by providing for the presence of an [antioxidant]" in rivastigmine, and also by identifying *preferred* antioxidants, it "implicitly acknowledges that there is a potential

[oxidation] issue." *Id*. And because that implicit recognition of the potential problem of oxidation is more than enough to show a motivation to combine under binding precedent, the district court's holding that the '807 patent would not have motivated a POSA to combine rivastigmine with an antioxidant must be reversed.

2. The absence of details about *how* or *when* to combine rivastigmine with an antioxidant does not undermine the motivation to do so.

a. Compounding its error, the district court reasoned that the '807 patent would not have motivated a POSA to combine rivastigmine with an antioxidant because the patent lacked details about exactly how or when to do so. Yet those purported omissions have nothing to do with the motivation to combine, and the district court's reliance on them simply underscores the need for reversal.

First, the district court noted that, "despite the laundry list of compounds that 'can be incorporated,' there is no specific example in the '807 patent combining RA7 with an antioxidant." A40. But neither the "laundry list" nor the absence of a "specific example" matters. As to the laundry list, "mere disclosure of alternative" combinations "does not teach a person of ordinary skill away from" the combinations that *are* "within the scope of [a] patent." *Allergan*, 754 F.3d at 964. Put another way, the fact "[t]hat the ['807] patent discloses a multitude" of other "combinations does not render [the] particular formulation" of rivastigmine and an

antioxidant any "less obvious." *Merck & Co. v. Biocraft Labs., Inc.*, 874 F.2d 804, 807 (Fed. Cir. 1989).

The same is true for the lack of any "specific example" illustrating the combination. Such "silence does not imply teaching away" and does not diminish "[a] motivation to combine" known elements that "may be implicit." *Allergan*, 754 F.3d at 964. "[E]ven though there is no specific example in the ['807 patent] directed to preparation" of rivastigmine with an antioxidant, there "is sufficient disclosure … to have rendered [it] obvious." *In re Baxter*, 656 F.2d 679, 684 (C.C.P.A. 1981).

Second, the district court found it insufficient that the '807 patent "discloses the addition of an antioxidant 'as required,'" because it does not affirmatively state that rivastigmine "requires an antioxidant." A40. But as we have shown, the proper legal standard for motivation does not require an explicit teaching.

Nor is it surprising that the '807 patent does not contain a categorical statement that rivastigmine always "requires an antioxidant." As the district court's own findings confirm, it is undisputed that rivastigmine does not *always* oxidize—it is only "*susceptible* to oxidative degradation." A24 (emphasis added). Whether it requires an antioxidant "depend[s] on the environment to which it is exposed." *Id.*; A2675-76. In fact, in related cases, the same judge held that other companies' generic versions of Novartis's rivastigmine patch did *not* contain an antioxidant

and therefore could not infringe Novartis's patents. *Novartis Pharms. Corp. v. Par Pharm., Inc.*, 2014 WL 4364674 (D. Del. Aug. 29, 2014); *Novartis Pharms. Corp. v. Alvogen Pine Brook Inc.*, No. 13-52-RGS (D. Del. July 7, 2014). The '807 patent's instruction to add an antioxidant "as required" is thus entirely expected.

Third, the district court found that the '807 patent does not render the combination of rivastigmine and an antioxidant obvious because it contains "no discussion of the appropriate *amount* of antioxidant, if required, to be used." A40 (emphasis added). But that "confus[es] obviousness with anticipation." *SIBIA Neurosciences*, 225 F.3d at 1357. "[W]hile anticipation requires all elements of a claim to be disclosed within a *single* reference," "[o]bviousness can be proven by *combining* existing prior art references." *Cohesive Techs., Inc. v. Waters Corp.*, 543 F.3d 1351, 1364 (Fed. Cir. 2008) (emphasis added). The "mere silence about a particular feature" in one reference is therefore immaterial to obviousness "if it is disclosed elsewhere in the prior art." *In re Haase*, 542 F. App'x at 967.

Here, the district court itself observed that another prior art reference, the *Handbook of Pharmaceutical Excipients*, "discloses the antioxidants claimed in the patents in suit, in amounts that fall within the claimed concentration ranges." A45. Likewise, the court confirmed that another prior art patent "teaches the inclusion of an antioxidant" in a transdermal patch, again "within the concentration ranges claimed in the patents in suit." *Id*. Because these references independently taught

"the appropriate amount of antioxidant" (A40), there was no need for the '807 patent to do so. Rather, "a patent need not teach, and preferably omits, what is well known in the art." *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384 (Fed. Cir. 1986).

Fourth, the court deemed the '807 patent insufficient to support an obviousness ruling because it "contains no stability data." A41. But that is irrelevant. "To conclude" that combining rivastigmine with an antioxidant "would have been obvious," the '807 patent "merely had to suggest" it. *Pfizer*, 480 F.3d at 1368 (quotations omitted). That a POSA must "verify through testing the expected traits" of particular formulations, including their exact "stability," is "of no consequence." *Id.* at 1367. Patentability cannot depend on that type of routine testing, which is "the work of a skilled artisan, not of an inventor" (*id*. at 1368), and "would occur in the ordinary course without real innovation" (*KSR*, 550 U.S. at 419).

b. At most, the lack of precise details about how or when to combine rivastigmine with an antioxidant relates to whether the prior art "enables one skilled in the art to make and use the claimed invention." *Streck, Inc. v. Res. & Diagnostic Sys.*, 665 F.3d 1269, 1288 (Fed. Cir. 2012) (quotation omitted). For "prior art patent[s]" like the '807 patent, however, courts must apply "a presumption … that both the claimed and unclaimed disclosures … are enabled" to a POSA. *Amgen*, 314 F.3d at 1355.

The district court was therefore required to presume that a POSA could make and use the compositions described in the '807 patent—including compositions of rivastigmine in which "antioxidants … can be incorporated as required." A1539 (7:48-50). It makes no difference that the '807 patent is silent about the particular circumstances of how or when to add such antioxidants. The answers to these questions were presumptively within a POSA's reach. Yet the district court never mentioned this legal presumption, let alone found that it had been rebutted.

In any event, even "a non-enabling" reference can be used in "determining obviousness," because it is "prior art for all that it teaches." *Symbol Techs., Inc. v. Opticon, Inc.*, 935 F.2d 1569, 1578 (Fed. Cir. 1991) (quotation omitted). If nothing else, the '807 patent both taught that "antioxidants … can be incorporated" with rivastigmine and identified "[p]referred antioxidants for use with" it. A1539 (7:48-53). It is undisputed that every other limitation of Novartis's patents—including each possible antioxidant to use, the amounts of them to use, and even their use in transdermal patches—was in the prior art and thus would have been known to a POSA. *Supra* at 12-14. Because Novartis's patents claim nothing "more than the predictable use" of rivastigmine and an antioxidant "according to their established functions," the district court's failure to find obviousness was reversible error. *KSR*, 550 U.S. at 417.

3. The '807 patent's reference to "greater chemical stability" relative to a highly unstable prior art compound does not counter the motivation to combine rivastigmine with an antioxidant.

The district court likewise erred in concluding that the '807 patent does not teach the addition of an antioxidant because it "portrays" the stability of RA7—the racemic mixture that contains 50% rivastigmine—"in a positive light" (A41). In support, the court cited the '807 patent's two statements that RA7 has "greater chemical stability than physostigmine," an older AChE inhibitor in the prior art. *Id.*; A1541 (11:26-35), A1537 (3:37-39). Both legally and factually, the court's reliance on these statements was unsupportable.

As a legal matter, statements do not "teach away" from a motivation to combine known elements unless they "criticize, discredit, or otherwise discourage investigation into the invention claimed." *Norgren Inc. v. Int'l Trade Comm'n*, 699 F.3d 1317, 1326 (Fed. Cir. 2012) (quotations omitted). By definition, a reference "does not … teach away" from something when it "provides a[] … preference" for it. *Allergan*, 754 F.3d at 964. Here, the '807 patent does not criticize or discredit the idea of combining rivastigmine with antioxidants. Rather, it says that such a combination is possible, and sometimes "required," and it specifically identifies "[p]referred antioxidants for use with" rivastigmine. A1539 (7:48-53). Thus, the '807 patent "specifically discloses a preference" for at least some antioxidants,

and "does not teach away from using" them—as a matter of law. *In re Chapman*, 595 F.3d at 1337-38.

As a factual matter, moreover, the district court misconstrued both the extent and the type of stability that the '807 patent "portrays" RA7 to have. As the court itself acknowledged, the '807 patent discusses RA7's stability only "relative to physostigmine." A41. But that is a low bar. As Novartis's expert conceded, physostigmine is "quite unstable," and he explained at length "[t]he reason that it's so unstable." A3261, A3321. Thus, a POSA would not read the '807 patent's statements about RA7's "greater chemical stability" to mean that RA7 *is* stable—only that it is somewhat "more stable" than another drug that is highly *un*stable. A2948-49, A3261.

Just as importantly, the '807 patent speaks only to RA7's "greater chemical stability" in *general*—it says nothing at all to suggest that RA7 has good *oxidative* stability. As the district court elsewhere recognized, "oxidative degradation is not the only degradation pathway," but just one among "many known types of degradation," including one called "hydrolysis." A39, A3090. Whereas "oxidation" refers to degradation by air, "hydrolysis" refers to "degradation by water." A3104. And unlike with oxidation, "[a]n antioxidant will not reduce a hydrolysis reaction." A3156. Rather, there are different types of "excipients" (i.e., inactive ingredients) "to prevent each of these types of degradation." A39.

As Novartis's own expert testified, hydrolysis is particularly relevant to the poor stability of physostigmine, which not only oxidizes but also "hydrolyze[s] readily." A3155. Rivastigmine, by contrast, is much more resistant to hydrolysis. In fact, when Novartis's patents were filed, its "stability towards hydrolysis" was known to be "more than 50,000" times better than physostigmine's. A3159.

Not so when it comes to *oxidative* degradation. There, a POSA would have expected the stability of physostigmine and rivastigmine to be very similar. As Novartis's expert admitted, both compounds share a particular type of chemical structure called a "tertiary amine," which is the part of the molecule "that is subject to oxidat[ive] degradation." A3215-16. And while that structure does not necessarily degrade in every environment, it was well known when Novartis's patents were filed that "tertiary amines are often oxidized." A2893, A3251-52.

Accordingly, a POSA would have understood the '807 patent's statement that rivastigmine has "greater chemical stability than physostigmine" to mean only that it is less susceptible to *hydrolytic* degradation—not that it is any less susceptible to *oxidative* degradation. If anything, based on the undisputed chemical similarity between rivastigmine and physostigmine (i.e., their shared tertiary amine structure), a POSA would have *expected* rivastigmine to oxidize—and thus would have been motivated to combine it with an antioxidant. Indeed, based on the same tertiary amine structure "present in the chemical structures of rivastigmine" and

another drug, "nicotine," the PTAB has preliminarily found that a POSA "would have understood" from "the chemical structure of rivastigmine" that it "was susceptible to oxidation." *Noven Pharms.*, No. IPR2014-00549 (Paper 10), at 13-14.[2]

* * * * *

In sum, the '807 patent plainly teaches that "antioxidants … can be incorporated as required" with rivastigmine, and even names "[p]referred antioxidants for use with" it. A1539 (7:48-53). Under *KSR* and this Court's repeated holdings that the motivation to combine known elements may be "implicit," that is more than enough to establish obviousness. And none of the omissions or statements in the '807 patent that the district court cited to avoid that conclusion are even relevant. Thus, the court's decision to uphold Novartis's patents must be reversed.

B. Elmalem independently and explicitly teaches both the problem and the solution that Novartis purportedly "discovered."

Even assuming that the '807 patent would not have alerted a POSA that rivastigmine is susceptible to oxidative degradation and should therefore be com-

[2] The district court also noted that the '807 patent was before the Patent Office during prosecution. A41. Quoting *Sciele Pharma Inc. v. Lupin Ltd.*, the court reasoned that Watson's "'invalidity contention is based upon the same argument on the same reference that the PTO already considered.'" *Id.* (quoting 684 F.3d 1253, 1260 (Fed. Cir. 2012)). But Watson's invalidity arguments are *not* "the same" as any "that the PTO already considered." In fact, during prosecution, the PTO failed to make *any* prior art rejections. A3109; *see* A746-1009. And regardless, *Sciele* confirms that "there is no heightened or added burden that applies to invalidity defenses that are based upon references that were before the Patent Office." 684 F.3d at 1260.

bined with an antioxidant, the Elmalem article—which was *not* before the Patent Office during prosecution—would have made that even clearer. Elmalem undeniably and specifically teaches the combination of RA7—and thus of rivastigmine—with sodium metabisulphite, a "very well-known antioxidant." A2892, A2938, A3164. Quite apart from the '807 patent, that fact alone easily establishes an implicit motivation to combine rivastigmine with an antioxidant. *Supra* at 34-35.

But there is more. Elmalem does not just confirm that rivastigmine *can* be, and *had been*, combined with an antioxidant. It explicitly teaches *why* an antioxidant is needed: "to prevent oxidation." A1876, A2931, A2948-50. Under settled law, Elmalem's "direct recommendation[] to use [an antioxidant] to minimize the risk[]" of oxidative degradation in rivastigmine "would have motivated one of ordinary skill in the art," with at least a reasonable expectation of success, to make and use Novartis's claimed invention. *Watson Pharms.*, 713 F.3d at 1376.

The district court held the opposite. Although Elmalem says an antioxidant was added "to prevent oxidation" of "[*a*]*ll* drugs"—including RA7 (A1876 (emphasis added))—the court concluded that the authors sought "to prevent oxidation" of only *one* drug, physostigmine (A42). As for RA7, the court found that the authors added an antioxidant only for a different, unstated reason: "to reduce variability" in their experiment. A43. That countertextual finding was wholly unsupportable.

For starters, there is no evidence that Elmalem's authors would have considered the presence or absence of an antioxidant to be a relevant "variable" in their experiment. In fact, Novartis's expert was unable to point to "anything that … indicates that Dr. Elmalem or her colleagues thought that [the antioxidant] would have an effect" on any test results. A3213. That alone warrants reversal.

Even setting aside the lack of evidence to support it, however, the district court's interpretation of Elmalem cannot be correct. If an antioxidant were added to RA7 only "to reduce variability," then it would also need to be added to the experiment's "saline placebo." A42-43. But that leads to two absurd results: *First*, since Elmalem's authors added antioxidants only to "drugs," the district court's interpretation requires saline to be a "drug"—contrary to both the plain meaning of the word and the plain text of Elmalem. *Second*, since Elmalem does not teach how *much* antioxidant to add to the plain saline, the district court's reading makes it impossible to reproduce the experiment—thus defeating one of the key purposes of scientific journal articles.

1. The district court's conclusion that Elmalem's authors added an antioxidant to rivastigmine only "to reduce variability"—and not, as they actually said, "to prevent oxidation"—is clearly erroneous.

As Novartis's own expert admitted, Elmalem "never describes a procedure" for "mixing saline with [an antioxidant]." A3209. In fact, the "Methods" section says that an antioxidant was added only to the "drugs"—not to the placebo.

A1876. Thus, it is undisputed that Novartis's theory "requires," in the words of the district court, "that saline be considered a drug." A43, A3207. To state that premise should suffice to refute it. Unfortunately, however, the district court bent over backwards to adhere to Novartis's "decidedly divergent" and supposedly "more nuanced" interpretation of Elmalem. A42. That was reversible error.

As Novartis's expert conceded, saline is nothing more than "table salt in water." A3164. Watson's expert agreed: Saline is only a "vehicle" for administering drugs—it "has no pharmacological effect" of its own and thus is "not a drug." A2945; *see Oxford English Dictionary* 1080 (vol. iv), 548 (vol. ix) (2d ed. 1989) (defining "drug" as "medicinal substance," i.e., "[h]aving healing or curative properties or attributes"); *Stedman's Med. Dictionary* 522 (26th ed. 1995) ("Therapeutic agent"); *Webster's Third New Int'l Dictionary of the English Language* 695, 1402 (1981) ("a substance used as a medicine," i.e., "a substance or preparation used in treating disease"); *The Random House Dictionary of the English Language* 438 (1966) ("a chemical substance administered to a person or animal to prevent or cure disease or otherwise enhance physical or mental welfare").

Elmalem's plain text confirms that its authors did not depart from the ordinary meaning of "drug." A2947. The article's section entitled "Drugs" lists "[t]he agents tested" as RA6, RA7, RA16, physostigmine, and morphine—not saline. A1876. The article then explains that "[a]ll drugs were made up freshly in sterile

saline." *Id.* As the district court acknowledged, "if the authors considered saline itself to be a drug," that sentence "does not make sense." A43 ("Saline is not mentioned as a drug in the 'Drugs' section of the paper, and it does not make sense that '[a]ll drugs were made up freshly in sterile saline' if the authors considered saline itself to be a drug."). We agree. Yet the court below was undeterred, and did not even try to resolve this paradox.

Instead, it relied on a single sentence—which appears only in the article's *abstract*—as evidence that "the study's use of the word 'drugs' includes … saline." A43. That sentence states: "'*Each drug*, RA6, (1 mg i.v., 2 mg s.c.) RA7 (1 or 2 mg i.v.); RA15 (0.25 or 0.5 mg i.v.), physostigmine (0.05 or 0.1 mg i.v.) ***or*** *saline* (1 ml), was injected simultaneously with morphine (8 mg i.v.) to groups of 6-10 rabbits.'" *Id*. (quoting A1875 (emphasis added).) But the district court's conclusion simply does not follow. Although the sentence includes both "drug" and "saline," it lists saline last and separates it from the drugs with a disjunctive "or"—confirming that "saline" is a *different* substance from "[e]ach drug."

In quoting this sentence, the district court declared that it was being faithful to the "punctuation … in [the] original" (A43), as if the absence of a comma before "or saline" could somehow redefine the word "drug" to include a saline placebo. The immediately preceding sentence shows that it does not: "This study compared the effects of 3 novel antiAChE agents … with that of physostigmine." A1875.

By starting the next sentence with "[e]ach drug," the authors simply referred back to those same compounds—and not to saline. Further, the abstract goes on to state: "Physostigmine … only antagonized the increase in paCO2 induced by morphine at 15 and 30 min. The drugs RA15 (0.5 mg), RA6 (2.5 mg) and RA7 (2mg) almost completely prevented the respiratory depression" (*id.*)—again, no mention of "saline" as a "drug."

That the authors were not adopting an unprecedented view that plain "saline" is a "drug" is further confirmed by the actual body of the article, which states: "Each of the following *drugs*, physostigmine (0.05 and 0.01 mg/kg); RA6 (0.5 and 1 mg/kg); RA7 (1 and 2 mg/kg) and RA15 (0.25 and 0.5 mg/kg), was injected intravenously (i.v.) with morphine (8 mg/kg) to groups of 6-10 rabbits per *drug*." A1876 (emphasis added). Saline is not even mentioned until the next sentence: "Nine *other* rabbits were given morphine alone with 0.1 ml/kg *saline*." *Id.* (emphasis added). Likewise, the next paragraph contrasts "each treatment group" of rabbits, which received "each of the above *drugs*," with the "*additional* rabbits" that were only "injected with *saline*." *Id.* (emphasis added).

As these passages show, nothing in Elmalem remotely overrides the ordinary meaning of "drug" or otherwise suggests that the authors added an antioxidant to saline. And since it is undisputed that they would have needed to do that if their reason for adding an antioxidant had been "to reduce variability" (A43), the district

court clearly erred in ignoring the authors' explicit statement that they added an antioxidant to RA7 for another reason: "to prevent oxidation" (A1876). In short, the district court's "decidedly divergent" reading of Elmalem was not "more nuanced" (A42)—it was clearly erroneous.

2. The district court's interpretation would also prevent the experiment in Elmalem from being reproduced, and thus cannot be correct.

The district court's error is further confirmed by the fact that its interpretation of Elmalem would make it impossible to reproduce the experiment that the article describes. It is well settled that "biological tests generally demand" methods that can "ensure accurate and reproducible results." *Embrex*, 216 F.3d at 1348. Indeed, Novartis's expert agreed that it is "certainly one of the purposes of the methods sections" in journal articles like Elmalem "to allow scientific peers to reproduce the work that is described." A3210-11.

If the district court's interpretation of Elmalem were correct, it would mean that the authors, in an effort "to reduce variability," added an antioxidant to the saline placebo. But if that were true, a POSA would not be able to reproduce their experiment, because the article does not disclose *how much* antioxidant to add to the saline. It discloses that amount only for the actual drugs. And for each drug, Elmalem instructs a POSA to use a *different* drug concentration, and to add an "equal weight" of antioxidant. A1876.

As Watson's expert explained, this means that the authors—in order "to make sure they had sufficient antioxidant" to provide "good protection" against oxidation for each of the "different concentrations" of drugs—added an amount of antioxidant that is "[e]quivalent to the weight of the drug that's in the solution." A2943. By contrast, the article gives no indication that *any* antioxidant—let alone some particular amount of it—was added to the saline placebo. A2944-45.

Below, Novartis attempted to avoid this problem by arguing that the term "equal weight" refers to some undisclosed amount of antioxidant that just happens to be "equal" for each formulation, including for the saline placebo. That is nonsense. When asked whether he could calculate how much antioxidant was added under that interpretation to "any of the[] solutions," Novartis's expert admitted: "No, I don't know." A3211. Under Watson's interpretation, by contrast, the same expert conceded that the experiment *would* be reproducible, because "[o]ne would be able to calculate" how much antioxidant was added to each drug. A3212.

The district court acknowledged these problems, yet sided with Novartis without even "attempting to explain scientifically why." A44. Instead, it simply "credit[ed] Novartis's accompanying trial testimony as being more credible." *Id.* But "[a] trial court makes a credibility determination in order to assess the candor of a fact witness, not to evaluate whether an expert witness' theory is supported by the … evidence." *Andreu ex rel. Andreu v. Sec'y of Dept. of Health & Human*

Servs., 569 F.3d 1367, 1379 (Fed. Cir. 2009). By abdicating its role of weighing the evidence and by adopting an interpretation that frustrates a core purpose of scientific publications, the district court committed reversible error.

C. Given the prior art's teachings about adding antioxidants to rivastigmine *specifically*, the district court erred by relying on prior art about the unpredictability of adding antioxidants to drugs *in general*.

Finally, the district court erred in assuming, as justification for its confined reading of the '807 patent and Elmalem, that a POSA "would not have been motivated to include an antioxidant in any formulation unless there was evidence of oxidative degradation." A39. That assumption was both irrelevant and incorrect as a matter of law.

It was irrelevant because "evidence of oxidative degradation" would have been discovered by *anyone* seeking to market rivastigmine—even without the guidance in the '807 patent and Elmalem. As Watson's expert explained in unrebutted testimony, routine stability tests outlined in FDA guidelines independently would have revealed "whether or not a particular composition required an antioxidant." A2978-79, A1521-33; *supra* at 14-15. Indeed, that is exactly how Novartis came up with "the addition of an antioxidant" here—less than a month after finding "degradation compounds" during those same "stability studies." A3052, A3075, A3057. Thus, even assuming that the "motivat[ion] to include an antioxidant" somehow turns on definitive "evidence of oxidative degradation" (A39), that

evidence would have been revealed—as it was to Novartis—"in the ordinary course" of obtaining FDA approval. *KSR*, 550 U.S. at 419.[3]

But even setting that point aside, the district court's assumption that a POSA would have needed such evidence before combining rivastigmine with an antioxidant was also legally flawed. The court based that assumption on its finding that antioxidants "can be incompatible with [a] drug or other excipients in [a] pharmaceutical composition, which could lead to a deleterious effect on the drug's performance." A39. "The compatibility of an excipient with a given pharmaceutical," the court explained, "cannot be predicted without experimentation." *Id.* And "due to the risk of incompatibility," the court found that the prior art as a whole discourages against using antioxidants, which "should only be included in a formu-

[3] Citing *Leo Pharm. Prods. v. Rea*, 726 F.3d 1346 (Fed. Cir. 2013), Novartis argued below that a stability problem that requires testing to be discovered can never motivate a POSA to combine known elements. But *Leo* involved wholly dissimilar facts. There, "the prior art consistently taught away from [the] combin[ation]"; the "solution" to the stability problem "was not predictable"; and the record "show[ed] 'extensive experimental evidence' of unexpected results." *Id.* at 1357-58. None of that is true here. Because the addition of an antioxidant "is not [an] unpredictable" solution, and "the prior art" does not "t[each] away from the combination," "the facts are unlike those in *Leo*." *Arlington Indus., Inc. v. Bridgeport Fittings, Inc.*, — F. App'x —, 2014 WL 4251552, at *3 (Fed. Cir. Aug. 29, 2014). And any broader reading of *Leo* would conflict with *KSR*'s teaching that "advances that would occur in the ordinary course without real innovation" are undeserving of "patent protection." 550 U.S. at 419.

lation if it has been proved that their use cannot be avoided." *Id.* (quotation omitted).

As a general proposition, that may be true. But whether it "is *generally* an unpredictable endeavor" to combine antioxidants and drugs "does not matter." *Allergan*, 754 F.3d at 965. Rather, "the question is more narrowly whether the success of using" antioxidants "would be reasonably []predictable" with *rivastigmine*. *Id.* The district court itself answered that question in the affirmative: Both the '807 patent and Elmalem "certainly disclose that an antioxidant *can* be added to RA7," and thus to rivastigmine. A38. In fact, each reference shows more than that—it confirms that antioxidants do not have any "deleterious effect on [rivastigmine]'s performance." A39.

First, Elmalem proves the successful combination of rivastigmine and an antioxidant with actual test results. As noted, Elmalem describes an experiment where a concentration of RA7 (i.e., 50% rivastigmine) was injected in rabbits together with "an equal weight" of a well-known antioxidant "to prevent oxidation." A1876; *supra* at 17-18. This particular combination of RA7 and an antioxidant "caused a maximum inhibition of more than 70%" of AChE that was "dose-related" in "all three regions" of the brain that were tested. A1877. And as Elmalem further notes, these results corroborated "previous findings with RA7" that fa-

vorably "demonstrated that AChE was inhibited[] to a significantly greater extent in the brain" than in other parts of the body. A1879.

As discussed in Novartis's patents and GB '040, rivastigmine's inhibition of AChE in the brain is what makes it "useful for the treatment of Alzheimer's disease." A733 (1:14-16), A741 (1:15-17); *supra* at 12. Because the testing data in Elmalem confirm that RA7 (and thus rivastigmine) is highly effective in inhibiting AChE even when combined with an antioxidant, Elmalem alone would have dispelled any theoretical concern that antioxidants could "be incompatible with" rivastigmine or have "a deleterious effect on the drug's performance." A39.

Second, the '807 patent further confirms the absence of any such incompatibility. As noted above, courts must apply "a presumption … that both the claimed and unclaimed disclosures in a prior art patent are enabled." *Amgen*, 314 F.3d at 1355. Here, therefore, the district court was required to presume that a POSA could make and use a pharmaceutical composition of rivastigmine in which "antioxidants … can be incorporated," at least when using the patent's "[p]referred antioxidants for use with" rivastigmine. A1539 (7:48-53). Just as critically, the court was required to presume that a POSA could make and use that pharmaceutical composition *without* impeding rivastigmine's therapeutic "useful[ness] for the treatment of … Alzheimer's disease." A1542 (13:1-5, cl. 4).

Given these presumptively enabling disclosures, any generalized "unpredictability" or concern about "a deleterious effect on … performance" (A39) is irrelevant. "Even if the [prior art] could be viewed as teaching away from the use of [antioxidants] *generally*, it would not cast doubt on" the compatibility of antioxidants with rivastigmine *in particular*. *Tyco Healthcare Group LP v. Mutual Pharm. Co., Inc.*, 642 F.3d 1370, 1376 (Fed. Cir. 2011) (emphasis added). In other words, even assuming "that it cannot be predicted how *any* [particular drug] will work" with an antioxidant, "this does not overcome" the prior art's "teaching that [rivastigmine specifically] *will* work" with an antioxidant. *In re Corkill*, 771 F.2d 1496, 1500 (Fed. Cir. 1985) (emphasis added).

The fact that the '807 patent and Elmalem discuss only two antioxidants—ascorbic acid and sodium metabisulphite—does not compel a different conclusion. As the district court construed the term, "antioxidant" broadly covers any "agent that reduces oxidative degradation." A11. "Given the breadth of [the] claimed invention," Watson "did not have the exacting burden" of showing that any "narrow class" of antioxidants was obvious, "let alone" any antioxidant "in particular." *Allergan*, 754 F.3d at 963. Instead, Novartis's patents are invalid if it was obvious to combine rivastigmine with "any" antioxidant. *Id*.

Moreover, even assuming that "the prior art … teach[es] that the addition" of antioxidants to rivastigmine only "*sometimes* works," that is sufficient to "pro-

vide[] the skilled artisan with a motivation to combine" the two. *Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1166-67 (Fed. Cir. 2006). "While there may be some antioxidants that would be relatively unsatisfactory, there would be no invention in trying those which are clearly indicated in the art as useful in the same relation, to determine whether or not those antioxidants can be used." *In re Gray*, 136 F.2d 742, 744 (C.C.P.A. 1943). That is "the work of a skilled artisan, not of an inventor." *Pfizer*, 480 F.3d at 1368.

CONCLUSION

Once it becomes clear that a POSA would have been motivated to combine rivastigmine and an antioxidant, it is inescapable that, as the district court put it, "the asserted claims … are invalid because the addition of an antioxidant to a pharmaceutical composition that oxidatively degrades is one of several known, obvious solutions." A46. The '807 patent and Elmalem each provide clear and convincing evidence to that effect. Together, their force is overwhelming. But even putting them aside, a combination that inevitably would have been identified by routine (and compulsory) testing "in the ordinary course" of drug development cannot be "[g]rant[ed] patent protection." *KSR*, 550 U.S. at 419.

The district court's judgment of patent validity should be reversed, and the asserted claims of the '031 and '023 patents held invalid as obvious.

Respectfully submitted,

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NOVEMBER 24, 2014

CERTIFICATE OF SERVICE

I certify that, on November 24, 2014, a true and correct copy of the foregoing *Brief for Defendants-Appellants* was caused to be served via email on counsel listed below:

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CERTIFICATE OF COMPLIANCE WITH TYPE-VOLUME LIMITATION, TYPEFACE REQUIREMENTS, AND TYPE STYLE REQUIREMENTS

1. This brief complies with the type-volume limitation of Federal Rule of Appellate Procedure 32(a)(7)(B) because it contains 13,790 words, excluding the parts of the brief exempted by Federal Rule of Appellate Procedure 32(a)(7)(B)(iii) and Federal Circuit Rule 32(b).

2. This brief complies with the typeface requirements of Federal Rule of Appellate Procedure 32(a)(5) and the type style requirements of Federal Rule of Appellate Procedure 32(a)(6) because this brief has been prepared in 14-point Times New Roman, a proportionally spaced typeface, using Microsoft Word 2010.

Dated: NOVEMBER 24, 2014

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ADDENDUM

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IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

NOVARTIS PHARMACEUTICALS CORPORATION, NOVARTIS AG, NOVARTIS PHARMA AG, NOVARTIS INTERNATIONAL PHARMACEUTICAL LTD. and LTS LOHMANN THERAPIE-SYSTEME AG,	:	
Plaintiffs,	:	Case No. 1:11-cv-01112-RGA
v.	:	Case No. 1:13-cv-00371-RGA
WATSON LABORATORIES, INC., WATSON PHARMA, INC., and ACTAVIS, INC.,	:	
Defendants.	:	

[PROPOSED] FINAL JUDGMENT

This matter having come before the Court for trial on the merits of all remaining issues in the above-captioned cases, namely to resolve the questions of whether Defendants Watson Laboratories, Inc., Watson Pharma, Inc. and Actavis, Inc. (collectively "Watson") infringe claims 3, 7, 13, 16 and 18 of U.S. Patent No. 6,335,031 ("the '031 Patent") and claims 2 and 7 of U.S. Patent No. 6,316,023 ("the '023 Patent"), and whether those claims are invalid by reason of obviousness; and the Court having heard the testimony of the fact and expert witnesses and having considered the documentary evidence and depositions submitted by the parties; and the Court having reviewed the post-trial briefs of the parties;

IT IS ORDERED AND ADJUDGED, for the reasons set forth in the Court's Trial Opinion dated June 18, 2014 (1:11-cv-01112-RGA, D.I. 40), that Final Judgment is hereby entered in District of Delaware Civil Action No. 1:11-cv-01112-RGA ("the 1112 suit") in favor

of Plaintiffs Novartis Pharmaceuticals Corporation, Novartis AG, Novartis Pharma AG, Novartis International Pharmaceutical Ltd. and LTS Lohmann Therapie-Systeme AG (collectively "Plaintiffs") and against Watson, finding that the rivastigmine transdermal products, 4.6 mg/24 hr and 9.5 mg/24 hr dosage strengths, that are the subject of Watson's Abbreviated New Drug Application ("ANDA") No. 202119 infringe claims 3, 7, 13, 16 and 18 of the '031 Patent and claims 2 and 7 of the '023 Patent, and that those claims are valid and not obvious; and it is further

ORDERED AND ADJUDGED, in view of Plaintiffs' and Watson's representations to the Court in connection with Watson's motion to deconsolidate the 1112 suit from District of Delaware Civil Action No. 1:11-cv-01077-RGA (1:11-cv-01077-RGA, D.I. 332 at 2; D.I. 371 at 3-4) that the issues in the 1112 suit are "identical" to the issues in District of Delaware Civil Action No. 1:13-cv-00371-RGA ("the 371 suit") and that the outcome in the 1112 and 371 suits "should be the same," that that Final Judgment is hereby entered in the 371 suit in favor of Plaintiffs and against Watson, finding that the rivastigmine transdermal product, 13.3 mg/24 hr dosage strength, that is the subject of Watson's ANDA No. 202119 infringes claims 3, 7, 13, 16 and 18 of the '031 Patent and claims 2 and 7 of the '023 Patent, and that those claims are valid and not obvious; and it is further

ORDERED AND ADJUDGED that Final Judgment is hereby entered in favor of Plaintiffs and against Watson on all counterclaims in the 1112 and 371 suits alleging and seeking declarations of no infringement and invalidity of the '031 Patent and/or the '023 Patent; and it is further

ORDERED that, pursuant to 35 U.S.C. § 271(e)(4)(A), the effective date of any final approval by the United States Food and Drug Administration of Watson's ANDA No.

202119 under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355 (j)) for the drug products for which approval is sought therein shall be a date not earlier than the January 8, 2019 expiration date of the '031 and '023 Patents; and it is further

ORDERED that, pursuant to 35 U.S.C. § 271(e)(4)(B), Watson, its officers, agents, servants, employees and attorneys, and those persons in active concert or participation with any of them, are enjoined until the January 8, 2019 expiration date of the '031 and '023 Patents from engaging in the manufacture, use, offer for sale, or sale within the United States, or importation into the United States, of any product covered by, or the manufacture or use of which is covered by, any claim of the '031 Patent or the '023 Patent; and it is further

ORDERED that the injunctive relief set forth in the two preceding paragraphs pursuant to 35 U.S.C. §§ 271(e)(4)(A) and 271(e)(4)(B) shall remain in full force and effect until the earliest of: (a) a further order of this Court modifying or vacating the injunctive relief; (b) a further order of the United States Court of Appeals for the Federal Circuit modifying, reversing or vacating the Court's judgment and/or injunctive relief to provide that Watson is not liable for infringement of any valid, asserted claim, or that all of the asserted claims are invalid; (c) the January 8, 2019 expiration date of the '031 and '023 Patents; and it is further

ORDERED that, in the event that Watson appeals this Final Judgment, any motion for attorneys' fees and/or costs under Fed. R. Civ. P. 54(d) and/or Local Rules 54.1 and/or 54.3, including any motion that this case is exceptional under 35 U.S.C. § 285, shall be considered timely if filed and served within thirty (30) days after final disposition of any such appeal; and it is further

ORDERED that, in the event that Watson does not appeal this Final Judgment, any motion for attorneys' fees and/or costs under Fed. R. Civ. P. 54(d) and/or Local Rules 54.1

and/or 54.3, including any motion that this case is exceptional under 35 U.S.C. § 285, shall be considered timely if filed and served within thirty (30) days after the expiration of the time for filing a notice of appeal under Fed. R. App. P. 3 and 4.

Dated this 4th day of Aug., 2014

Honorable Richard G. Andrews
United States District Court Judge

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

NOVARTIS PHARMACEUTICALS CORPORATION, NOVARTIS AG, NOVARTIS PHARMA AG, NOVARTIS INTERNATIONAL PHARMACEUTICAL LTD., and LTS LOHMANN THERAPIE-SYSTEME AG, Plaintiffs, v. PAR PHARMACEUTICAL, INC., Defendant.	Civil Action No. 11-1077-RGA (Consolidated)
NOVARTIS PHARMACEUTICALS CORPORATION, NOVARTIS AG, NOVARTIS PHARMA AG, NOVARTIS INTERNATIONAL PHARMACEUTICAL LTD., and LTS LOHMANN THERAPIE-SYSTEME AG, Plaintiffs, v. WATSON LABORATORIES, INC., WATSON PHARMA, INC., and ACTAVIS, INC., Defendants.	Civil Action No. 11-1112-RGA

TRIAL OPINION

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Attorneys for Defendants Watson Laboratories, Inc., *et al.*

June 18, 2014

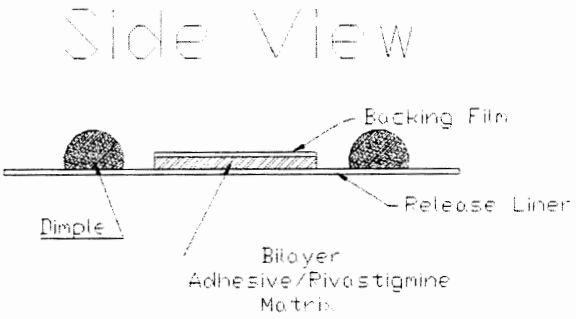
ANDREWS, U.S. DISTRICT JUDGE:

Novartis Pharmaceuticals Corporation, Novartis AG, Novartis Pharma AG, Novartis International Pharmaceutical Ltd., and LTS Lohmann Therapie-Systeme AG (collectively, "Novartis" or "Plaintiff") brought this suit against Watson Laboratories, Inc., Watson Pharma, Inc., Watson Pharmaceuticals, Inc. (collectively "Watson" or "Defendant"), and Par Pharmaceutical, Inc.[1] alleging infringement of U.S. Patent Nos. 6,335,031 ("the '031 patent") and 6,316,023 ("the '023 patent") (collectively, "the patents in suit"). Both patents share the same specification.[2] The '031 and '023 patents claim pharmaceutical compositions, transdermal devices, and methods of stabilizing compositions comprising the drug rivastigmine, which is an acetylcholinesterase inhibitor, and an antioxidant. (D.I. 310, p. 1). Novartis sells an Exelon® transdermal patch for the treatment of Alzheimer's disease that contains rivastigmine. Novartis listed the '031 and '023 patents in the Food and Drug Administration's "Approved Drug Products with Therapeutic Equivalence Evaluations," frequently referred to as the "Orange Book," as covering the Exelon® patches. Watson's Abbreviated New Drug Application 202,119 ("ANDA") seeks approval to engage in the commercial manufacture, importation, use, or sale of a transdermal patch containing rivastigmine and an antioxidant prior to the expiration of the patents in suit.

Watson's ANDA product is a transdermal patch that contains a backing film, an adhesive bilayer comprised of a 905A adhesive and a 900A adhesive, and a protective release liner, a schematic of which is shown below:

[1] Both the Par and Watson defendants were scheduled for trial beginning on August 26, 2013. Par and Novartis informed the Court on the morning of the first day of trial that a settlement had been reached. Relying on this representation, the Court entered an order staying the action with respect to Par for forty-five days and dismissed Par from the trial. (D.I. 293). The settlement later fell through, and a trial for Par and Novartis took place on May 1, 2014.

[2] Unless otherwise noted, all citations to the specification refer to the '031 patent.



(JTX 56, p. 1822-23). The process for manufacturing Watson's ANDA product can be summarized as follows: 1) the 905A adhesive and rivastigmine, the active ingredient, are mixed to form the 905A casting solution; 2) the 905A casting solution is applied to a polyester release liner, which is subsequently passed through a drying oven; 3) the 900A adhesive is applied to a polyester release liner and passed through a drying oven; 4) the release liner for the 905A layer is removed and the exposed 905A layer is laminated onto the 900A layer, thereby forming the adhesive bilayer; 5) the adhesive bilayer is then cut to size, packaged, and heat sealed into pouches. (*Id.*, pp. 1832-34). Watson's ANDA product is available in 5 and 10 square centimeter sizes. (*Id.*).

Novartis asserts that Watson's ANDA products infringe claims 3, 7, 13, 16, and 18 of the '031 patent and claims 2 and 7 of the '023 patent. Watson counters that the asserted claims are obvious under 35 U.S.C. § 103(a) and not infringed. The Court held a four day bench trial from August 26-29, 2013. (D.I. 306, 307, 308 & 309). As explained below, Novartis proved that Watson's ANDA products infringe by a preponderance of the evidence, and Watson did not prove by clear and convincing evidence that the asserted claims were invalid as obvious.

I. INFRINGEMENT

The five asserted claims in the '031 patent depend from non-asserted independent claims 1, 11, and 15, which are drawn to pharmaceutical compositions, transdermal devices, and a stabilization method, respectively. Claim 1 of the '031 patent recites:

> A pharmaceutical composition comprising:
> (a) a therapeutically effective amount of (S)-N-ethyl-3-{(1-dimethylamino)ethyl}-N-methyl-phenyl-carbamate in free base or acid addition salt form (Compound A);
> (b) about 0.01 to about 0.5 percent by weight of an antioxidant, based on the weight of the composition, and
> (c) a diluent or carrier.

'031 patent, claim 1. In the claim language "Compound A" refers to rivastigmine, the "S" enantiomer of the racemic compound RA_7.[3] Claim 3 narrows the pharmaceutical composition to those in which the antioxidant is "tocopherol, esters thereof, ascorbic acid, butylhydroxytoluene, butylhydroxyanisole or propyl gallate." Claim 7 recites a "transdermal device comprising a pharmaceutical composition as defined in claim 1, wherein the pharmaceutical composition is supported by a substrate."

The requirements of claim 11 are as follows:

> A transdermal device comprising a backing layer, a layer comprising a therapeutically effective amount of (S)-N-ethyl-3-{(1-dimethylamino)ethyl}-N-methyl-phenyl-carbamate (Compound A) and an amount of antioxidant effective to stabilize Compound A from degradation in a polymer matrix, a release-liner and, disposed between the layer comprising Compound A in a polymer matrix and the release-liner, a discrete layer of adhesive material for releasably fixing said transdermal device to a patient's skin.

[3] N-ethyl-3-{(1-dimethylamino)ethyl}-N-methyl-phenyl-carbamate, abbreviated as "RA_7," is a racemate. A racemate is a compound that is composed of two enantiomers of a chiral molecule, denoted as "S" and "R." The two enantiomers are identical in all respects except for the fact that they are mirror images of each other. (Tr. 67:17-69:1).

Id., claim 11. Claim 13 limits the identity of the antioxidant in the transdermal device to "tocopherol, esters thereof, ascorbic acid, butylhydroxytoluene, butylhydroxyanisole or propyl gallate."

Claim 15 recites:

> A method of stabilizing (S)-N-ethyl-3-{(1-dimethylamino)ethyl}-N-methyl-phenyl-carbamate in free base or acid addition salt form (Compound A), wherein the method comprises forming a composition by combining Compound A with an amount of antioxidant effective to stabilize Compound A from degradation.

Id., claim 15. Claim 16 limits the method's antioxidant to "tocopherol, esters thereof, ascorbic acid, butylhydroxytoluene, butylhydroxyanisole or propyl gallate," and claim 18 limits the amount of antioxidant to "about 0.01 to about 0.5% by weight based on the weight of the composition."

Two claims from the '023 patent, claims 2 and 7, are also asserted by Novartis. Claim 2 depends from claim 1, which recites:

> A pharmaceutical composition comprising 1 to 40 weight percent of (S)-N-ethyl-3-[(1-dimethylamino)ethyl]-N-methylphenyl carbamate in the form of a free base or acid addition salt, 0.01 to 0.5 weight percent of an antioxidant, and a diluent or carrier, wherein the weight percents are based on the total weight of the pharmaceutical composition.

'023 patent, claim 1. Claim 2 limits the composition of claim 1 to those where the antioxidant is "tocopherol, esters of tocopherol, ascorbic acid, esters of ascorbic acid, butylhydroxytoluene, butylhydroxyanisole, propyl gallate, and combinations thereof." Independent claim 7 requires:

> A transdermal device comprising a pharmaceutical composition comprising 1 to 40 weight percent of (S)-N-ethyl-3-[(1-dimethylamino)ethyl]-N-methylphenyl carbamate in the form of a free base or acid addition salt, 0.01 to 0.5 weight percent of an antioxidant, and a diluent or carrier, wherein the weight percents are based on the total weight of the pharmaceutical composition.

Id., claim 7.

The claims asserted by Novartis can be broken down into two groups: the "presence" claims and the "function" claims. Claims 3 and 7 of the '031 patent, as well as claims 2 and 7 of the '023 patent, constitute the presence claims. These claims require proof that Compound A and an antioxidant are present. The Court defined "antioxidant" as an "agent that reduces oxidative degradation." (D.I. 250, pp. 1-2). There is no additional requirement that the antioxidant function with respect to Compound A because that is specifically required in the function claims. (*Id.*, p. 2 ("The patents repeatedly disclose the combination of Compound A and the antioxidant without specifically requiring that the antioxidant affect Compound A. It would be improper to preclude those embodiments by limiting 'antioxidant' to require that interaction." (internal citations omitted))).

Claims 13, 16, and 18 of the '031 patent are referred to as the function claims. All three claims require "an amount of antioxidant effective to stabilize compound A from degradation," which the Court construed to mean, "an amount of antioxidant that will significantly reduce degradation of Compound A over a prolonged period of time." (*Id.*, pp. 2-3). The function claims, therefore, have an additional requirement that the antioxidant interact with Compound A to reduce degradation. The Court also construed "stabilizing" to mean "significantly reducing degradation over a prolonged period of time." (*Id.*, p. 3). These three terms are the only ones at issue, and the parties agree that the remaining elements of the asserted claims are met. (D.I. 310, pp. 29-30).

In its post-trial briefing, Watson contends Novartis failed to prove infringement of the presence claims because those claims have a functional limitation and Novartis never proved that Watson's product contains an agent that reduces oxidative degradation of any component. (D.I. 318, pp. 1-2). Watson asserts it does not infringe the function claims because the testing

conducted by Novartis's experts does not prove that Watson's ANDA product is an oxidative environment or that it contains a functioning antioxidant.

A. Legal Standard

"Under [35 U.S.C.] § 271(e)(2)(A), a court must determine whether, if the drug were approved based upon the ANDA, the manufacture, use, or sale of that drug would infringe the patent in the conventional sense." *Glaxo, Inc. v. Novopharm, Ltd.*, 110 F.3d 1562, 1569 (Fed. Cir. 1997). The application of a patent claim to an accused product is a fact-specific inquiry. *See Kustom Signals, Inc. v. Applied Concepts, Inc.*, 264 F.3d 1326, 1332 (Fed. Cir. 2001). Literal infringement is present only when each and every element set forth in the patent claims is found in the accused product.[4] *See Southwall Techs., Inc. v. Cardinal IG Co.*, 54 F.3d 1570, 1575-76 (Fed. Cir. 1995). The patent owner has the burden of proving infringement by a preponderance of the evidence. *Envirotech Corp. v. Al George, Inc.*, 730 F.2d 753, 758 (Fed. Cir. 1984) (citing *Hughes Aircraft Co. v. United States*, 717 F.2d 1351, 1361 (Fed. Cir. 1983)). Infringement can be shown by "any method of analysis that is probative of the fact of infringement," and, in some cases, "circumstantial evidence may be sufficient." *Martek Biosciences Corp. v. Nutrinova, Inc.*, 579 F.3d 1363, 1372 (Fed. Cir. 2009).

B. Findings of Fact

1. Butylhydroxytoluene ("BHT") is a well-known antioxidant.
2. BHT is present in Watson's ANDA product.
3. BHT is present in an amount between 0.01 and 0.5 percent by weight.
4. Rivastigmine is subject to oxidative degradation in an oxidative environment.
5. The presence of oxygen, peroxides, or other free radical generators creates an oxidative environment.

[4] There are no assertions of infringement by the doctrine of equivalents.

6. Oxygen, peroxides, and other free radical generators are present in Watson's ANDA product.

7. Watson's ANDA products show only minimal degradation of rivastigmine over a prolonged period of time.

8. BHT acts as an antioxidant to protect rivastigmine from oxidative degradation.

9. Watson's ANDA product infringes all asserted claims of the '023 and '031 patents.

C. Conclusions of Law

1. The Presence Claims

a. The presence claims do not require a functioning antioxidant

The three limitations of the presence claims are: Compound A, a certain weight percent of antioxidant, and a diluent or carrier. *See, e.g.*, '031 patent, claim 1. Unlike the function claims, nowhere in the presence claims is any function of the antioxidant mentioned. *Compare id.* (requiring Compound A and "about 0.01 to about 0.5 percent by weight of an antioxidant"), *with id.*, claim 11 (reciting Compound A "and an amount of antioxidant *effective to stabilize Compound A* from degradation" (emphasis added)). The Court cautioned in its claim construction opinion that it would be "improper to impute the antioxidant's stabilizing effect on Compound A, explicitly claimed in some claims [*i.e.,* the function claims], into claims that do not contain that explicit limitation [*i.e.*, the presence claims]." (D.I. 250, p. 2). Despite this clear statement, Watson maintains that "antioxidant," as used in the patents in suit, "requires the presence of an agent that reduces oxidative degradation of some component in the claimed composition." (D.I. 318, pp. 12-13 ("The definition of 'antioxidant' adopted by the Court, 'an agent that reduces oxidative degradation,' plainly recognizes that the term is a functional limitation that requires a reduction of oxidative degradation in the claimed composition.")). This argument is rejected as being inconsistent with the Court's claim construction.

b. Watson's ANDA products meet every limitation of the presence claims

The parties agree that Watson's ANDA product contains Compound A (PTX 311, p. 1603) and a diluent/carrier. (JTX 56, p. 1823). Only the second limitation requiring "0.01 to 0.5 weight percent" of an antioxidant is in dispute.[5]

Butylhydroxytoluene, or BHT, is well known in the art as an antioxidant. (DTX 11, p. 47; PTX 17, p. 203; JTX 184, p. 1261; JTX 19, p. 441; DTX 55, p. 263). The patents in suit also identify BHT as an antioxidant in the specification and claim BHT as an antioxidant in the asserted claims. '031 patent, 4:11-14 ("The applicant has found that an effective stabilising effect is surprisingly achieved when the antioxidant is selected from . . . butylhydroxytoluene."); *id.*, claim 3 ("A pharmaceutical composition according to claim 1 wherein the antioxidant is . . . butylhydroxytoluene."). Novartis's infringement expert, Dr. Davies, performed tests[6] on Watson's ANDA products that identified the presence of BHT. (Tr. 312:15-21). Watson's expert, Dr. Sessler, admitted that Watson's ANDA products contain BHT (Tr. 398:21-399:1), and Watson itself conceded that BHT may have been introduced into its product by an upstream supplier. (D.I. 318, p. 6 n.2 ("It appears that BHT may have been added to the tackifier component by one of Henkel's suppliers upstream in the polymer manufacturing process and that small amounts of BHT were carried over into Watson's ANDA product as an unreactive impurity.")). This evidence proves that BHT, a well-known antioxidant, is present in Watson's ANDA products.

BHT is present in Watson's ANDA products within the claimed ranges: 0.01 to 0.5 percent by weight of the composition. Dr. Davies tested the 905A adhesive in isolation using gas

[5] Claim 1 of the '031 patent requires "about" 0.01 to "about" 0.5 percent by weight. This difference is immaterial because, as shown below, the measured amount of antioxidant falls within the 0.01 to 0.5 weight percent range.
[6] The tests Dr. Davies utilized were gas chromatography and gas chromatography coupled with mass spectrometry. (Tr. 311:21-312:21).

chromatography and found BHT at a level of 447 parts per million, which is 0.045 percent. (JTX 41, p. 2; JTX 36; Tr. 320:7-20). After the addition of rivastigmine to the 905A adhesive layer, the BHT concentration is decreased to 0.032 percent. (JTX 41, p. 2; Tr. 320:10-321:17). Dr. Davies then performed the same tests on the 905A/900A adhesive bilayer and measured 0.027 percent BHT. (JTX 41, p. 2; JTX 36). Using these result, Dr. Davies calculated[7] the amount of BHT in the drug-containing 905A layer in two scenarios: 1) all of the BHT remains in the 905A layer but the rivastigmine becomes distributed throughout the 905A/900A adhesive bilayer via diffusion;[8] and 2) BHT and rivastigmine both diffuse and become evenly distributed in the 905A/900A adhesive bilayer. (JTX 41, pp. 1-2). The amount of BHT in the 905A layer under those two scenarios is 0.036 and 0.023 percent by weight, respectively. (*Id.*, p. 2; Tr. 113:15-120:6). In response to criticism from Dr. Sessler, Dr. Davies repeated his experiments using high performance liquid chromatography and ultraviolet spectroscopy. (Tr. 329:13-330:8). These additional tests showed "excellent agreement" with the gas chromatography results and confirmed his earlier findings. (*Id.* at 330:4-14; JTX 51).

In addition to Dr. Sessler's criticism, Watson advances several other arguments in support of its non-infringement position. Watson points out that "BHT is not identified in any of Watson's product development reports for the formulation used in Watson's ANDA product, and BHT is not mentioned anywhere in Watson's ANDA." (D.I. 318, p. 6). The fact that those reports did not detect and quantify BHT does not mean no BHT is present. Novartis has shown,

[7] Dr. Davies was not able to measure the diffusion of BHT experimentally because the BHT level is below the instrument's limit of detection. (Tr. 328:10-16). Nonetheless, there are several reasons to believe that BHT will diffuse. First, there is no barrier to diffusion between the 905A and 900A adhesive layers. Second, Dr. Davies experimentally confirmed that rivastigmine diffuses through the bilayer. Third, BHT is a smaller molecule than rivastigmine which, generally speaking, means it will more readily diffuse. (Tr. 121:17-122:22).

[8] The adhesive bilayer is a highly diffusible system, allowing the rivastigmine to travel from the 905A layer through the 900A layer and into the patient's skin. (Tr. 323:15-324:7). Dr. Davies confirmed the diffusion of rivastigmine experimentally through Raman spectroscopy. (Tr. 323:15-329:3; JTX 38).

and Watson now appears to admit (*id.*, p. 6 n.2), that Watson's ANDA products contain BHT. How the BHT entered Watson's product and why previous reports did not quantify the amount of BHT is irrelevant for purposes of infringement. Watson also asserts that Novartis should have conducted additional testing for "BHT daughter products" to prove that the BHT in Watson's ANDA product actually functioned as an antioxidant. (*Id.*, pp. 29-30). This line of testing is not necessary because, as discussed above, the presence claims do not add a functional limitation vis-à-vis the antioxidant.

In summary, the amount of BHT, a known antioxidant, present in both scenarios evaluated by Dr. Davies falls within the amount required in the asserted claims. Watson does not dispute that its ANDA product meets the other claim limitations. (D.I. 310, p. 30). Therefore, Novartis has proven by a preponderance of the evidence that Watson's ANDA product infringes the presence claims of the patents in suit.

2. The Function Claims

As explained by the Federal Circuit, patentees are permitted to prove infringement by "any method of analysis that is probative of the fact of infringement, and circumstantial evidence may be sufficient." *Martek Biosciences Corp.*, 579 F.3d at 1372-73 (internal citation omitted) (finding combination of testing and scientific literature sufficient to prove infringement). According to Watson, Novartis must establish the following three elements to prove infringement of the function claims: "(1) rivastigmine oxidatively degrades in Watson's product; (2) BHT is significantly reducing the oxidative degradation of rivastigmine in Watson's product; and (3) the significant reduction of the oxidative degradation of rivastigmine occurs over a prolonged period of time." (D.I. 318, p. 13). Here, Novartis has proven that free radical generators create an oxidative environment, that Watson's ANDA products contain three known

free radical generators, and that rivastigmine is susceptible to oxidative degradation in the presence of those free radical generators. Despite this oxidative environment, the rivastigmine in Watson's ANDA products undergoes only minimal oxidative degradation over a prolonged period of time. The most logical conclusion is that the BHT in Watson's ANDA products acts as an antioxidant by scavenging free radicals, thereby protecting rivastigmine from oxidative degradation.

a. Watson's ANDA product is an oxidizing environment

Watson's ANDA product is manufactured and stored in an oxidative environment. Oxidative degradation is a type of chemical reaction, caused by the presence of free radicals, "where the substance that is oxidized loses an electron to another substance that is called an oxidant." (Tr. 134:22-135:9). Free radicals are a highly reactive species due to their free or unpaired electrons. (*Id.* at 135:15-19). Species with paired electrons are more stable, so free radicals take electrons from other molecules to pair their free electrons. (*Id.* at 135:20-24). Oxygen, peroxides, and other free radical generators, which include residual monomers, are three common sources of free radicals. (*Id.* at 136:14-137:12). Importantly, chain reactions do not require large quantities of free radicals. (*See, e.g.*, JTX 188, p. 1507 ("Only a very small amount of oxygen is required to initiate a chain reaction."); Tr. 136:22-137:4). Watson's ANDA product is exposed to all three categories of free radical generators, which creates an oxidative environment. The presence of each free radical generator will be discussed in turn.

Every step of Watson's manufacturing process is carried out in the presence of air, which contains oxygen. Rivastigmine is mixed with the 905A adhesive in ambient air, the 905A casting solution is passed through a filter in ambient air, the 905A casting solution is coated onto the release liner in ambient air, the 905A-coated release liner is dried in the presence of "filtered

and heated air," the backing layer is laminated onto the 905A adhesive in ambient air, the 900A casting solution is coated onto the release liner in ambient air, the 900A-coated release liner is dried in the presence of "filtered and heated air," and the 900A and 905A adhesive layers are laminated together in ambient air. (JTX 56, pp. 1832-37). The individual product patches are also cut and pouched in ambient air. (*Id.*). Indeed, Dr. Sessler acknowledged during cross-examination that the external environment for each step of the manufacturing process occurs in ambient air. (Tr. 513:4-518:19). It should come as no surprise, therefore, that Dr. Davies found the presence of oxygen inside the pouch containing Watson's ANDA product in a concentration comparable to that of ambient air. (JTX 54, p. 2; Tr. 339:22-330:14).

Watson raises two counterarguments questioning whether the manufacturing process's environment is indicative of the oxygen levels in the ANDA product itself. First, Dr. Sessler emphasized that pressurized nitrogen is used to extrude the 905A and 900A adhesive solutions onto the release liners, thereby forming a "nitrogen-saturated solution." (Tr. 514:10-515:21). Although the nitrogen gas does not stay in the adhesive layer, Dr. Sessler testified that he believed "a blanket of vapor and nitrogen" would form around the adhesive and protect it from oxygen molecules. (*Id.* at 453:2-23). Dr. Sessler did not provide any support for this argument other than the general scientific principle that gas solubility decreases at higher temperature, which would lead to the "out gassing" of nitrogen from the adhesive. (*Id.*). Even if Dr. Sessler was correct in his hypothesis about the nitrogen blanket, the nitrogen blanket would only protect the adhesive from oxygen for the steps following extrusion. There would be no nitrogen blanket for any of the previous steps, each of which was conducted in the environment of ambient air.

Second, Watson criticized Dr. Davies for failing to determine whether oxygen is present in the adhesive bilayer itself. (D.I. 318, p. 15). Dr. Davies was unable to perform direct testing

on the adhesive bilayer both because the bilayer was too thin (on the order of 90 microns thick) and because placing the needle into the bilayer would block the sensor. (Tr. 351:11-22). Novartis did, however, link the oxygen concentration in the pouch to the oxygen concentration in the adhesive bilayer. The backing layer used in Watson's ANDA product is described by the manufacturer as having "high oxygen transmission rates." (JTX 24, p. 2652; Tr. 165:7-15). Dr. Klibanov, another Novartis expert, testified that the oxygen present in the pouch will "readily penetra[te]" the backing film and enter Watson's ANDA product. (Tr. 165:7-166:15). Indeed, Dr. Sessler agreed that these transdermal patches are *designed* for air to permeate the patch to enhance skin health, which requires that the backing layer allow for the diffusion of oxygen. (*Id.* at 522:13-22). Therefore, it is a logical conclusion that the gases in the pouch, which include oxygen, will enter into Watson's ANDA product.

Watson's ANDA products also contain peroxides. The peroxide value, or peroxide number, test is a well-known method for detecting peroxides. U.S. Patent No. 6,699,498, 2:58-62 ("the '498 patent") ("The peroxide content is commonly expressed by means of the so-called peroxide number."). As described in the U.S. Pharmacopeia, the test "expresses, in milliequivalents of active oxygen, the quantity of peroxide contained in 1000 g of the substance." (JTX 47, p. 152). Using this standard experiment, Dr. Davies tested samples of both the 900A and 905A bulk adhesives and found the presence of peroxides. (JTX 53, p. 2 (noting peroxide values of 1.64 and 1.89 for the 900A adhesive and 0.72 and 1.07 for the 905A adhesive); Tr. 353:17-354:20). In addition to Dr. Davies's testing, Novartis relies on two documents from Henkel, Watson's adhesive manufacturer, showing that peroxides are used in the manufacture of the adhesive and might remain after manufacturing is complete. Henkel lists t-amylperoxypivalate ("TAPP"), a known peroxide, as an ingredient in the 900A adhesive whose

purpose is to scavenge residual monomers. (JTX 23, p. 1; Tr. 174:13-175:5). Moreover, a Henkel employee informed Watson in an email that the 900A adhesive "contains trace amount[s] of residual initiator, which is a peroxide" when Watson inquired about the 900A components. (JTX 32, p. 285088).

Watson offers three arguments in rebuttal. First, Watson contends that the peroxide test used by Dr. Davies does not measure for peroxides. (D.I. 318, p. 17). Watson is technically correct because the peroxide test actually measures the extent to which iodide ions can be oxidized to iodine. However, as Dr. Klibanov explained, the test is conducted under conditions where the measured oxidation is attributable to the presence of peroxides. (Tr. 286:3-287:4 ("Q. So it's a bit of a misnomer to say [the peroxide value test] measures peroxide. It is not directed to peroxides; correct? A. No. I disagree with that. Q. All right. Well, you wouldn't disagree that what it actually measures is the extent to which iodide is oxidized to iodine? A. Yes, but it's done under the conditions where what you measure is a peroxide. That's the test that is described by the United States Pharmacopeia specifically to determine peroxide oxidation number.")). Watson believes this is problematic because there are numerous substances other than peroxides that can oxidize iodide to iodine but that are incapable of oxidizing rivastigmine. (D.I. 318, p. 17; Tr. 429:22-430:16). Despite flagging this as a potential issue, neither Dr. Sessler in his trial testimony, nor Watson in its post-trial briefing, offered any scientific literature in support of its position that this test was applied improperly. Watson's unsubstantiated argument is not persuasive in light of the U.S. Pharmacopeia and a U.S. patent on transdermal devices that both list the peroxide value test as a standard method for determining the quantity of peroxides. (JTX 47, p. 152; '498 patent, 2:58-62; *see also* Tr. 354:7-11).

Second, Watson asserts the tests Dr. Davies conducted on the samples of bulk 900A and 905A adhesive have no bearing on the peroxide level in Watson's ANDA product. (D.I. 318, p. 17). This, too, is unpersuasive because Dr. Davies explained that testing the adhesives themselves prior to their inclusion in the transdermal device is the standard approach. (Tr. 354:21-355:15). Dr. Sessler agreed on cross examination that the method used by Dr. Davies is taught in the '498 patent, which addresses transdermal systems. (Tr. 526:16-527:9; '498 patent, 3:24-42). In addition, Dr. Davies testified that it would not be practical for him to test the actual ANDA product because he would have to remove the adhesive bilayer from the product. (Tr. 355:16-356:13). This process is difficult and would require roughly 150 patches to obtain enough material to conduct a single test. (*Id.*). Moreover, Dr. Klibanov noted that Watson did not take any steps to remove the peroxides from either the 900A or 905A adhesive layer, so it stands to reason that the peroxides will still be present when those two peroxide-containing layers are combined to form a bilayer. (*Id.* at 179:7-18).

Finally, Watson disagrees over the import of the Henkel documents cited by Novartis. The fact that Henkel uses TAPP in the manufacturing process proves nothing, according to Watson, because TAPP is used as a monomer scavenger. (D.I. 318, p. 20). Monomer scavengers are consumed during the manufacturing process so Watson posits there is no reason to believe that TAPP carries over to the ANDA product,[9] and Novartis did not conduct any tests to confirm its theory. (Tr. 439:13-24). It is true that Novartis did not perform experiments to determine if residual TAPP is present in Watson's ANDA product. The identity of the particular peroxide(s) present in Watson's ANDA product, however, is immaterial. Novartis has shown through Dr. Davies's experiments that a measureable amount of peroxide is present, and this is

[9] Although not dispositive, the certificate of analysis for the 900A adhesive does not list TAPP as a component. (JTX 186, p. 2644; Tr. 255:13-256:10).

sufficient to conclude that Watson's ANDA product is at least a minimally oxidative environment.[10] Watson also criticizes the Henkel email as informal hearsay from someone who was never deposed and who did not testify at trial. (D.I. 318, p. 20). In concluding that Watson's ANDA product contains peroxides, the Court does not rely on the Henkel email alone. The email is simply one piece of evidence, corroborated by Dr. Davies's experimental findings, indicating peroxides are present. It should also be noted Watson offered no objection to the exhibit at trial. (Tr. 173:11-174:2).

Residual monomers, a type of free radical generator, are present in Watson's ANDA product. Henkel's specification document for the 900A adhesive states that "residual levels of the starting monomers may be present in the final product" because polymerization "is never 100% efficient." (JTX 23, p. 1). There is a section of the specification titled "Residual Monomers" that lists the maximum specified limits for each monomer that can be present. (*Id.*). Some of these limits for the individual monomers are as high as 700 ppm, and if all listed monomers were present in their maximum specified amounts it would exceed 1500 ppm. (*Id.*). Another Henkel document, the certificate of analysis, lists what is actually present in the product, as opposed to the specification which denotes what is permitted in the product. (Tr. 182:3-13). The certificate of analysis for the 900A adhesive identified the presence of four residual monomers at a combined concentration of 606 ppm. (JTX 186, p. 2644; Tr. 182:3-184:12; *see also* JTX 30, p. 279745 (reporting 388 ppm of residual monomers in a different batch of 900A adhesive)).

Watson does not substantively dispute that residual monomers are present in its ANDA products. Instead, Watson contends the amount of residual monomers is insufficient to cause

[10] Watson's arguments regarding whether the peroxides have the "power" to oxidatively degrade rivastigmine are addressed below.

rivastigmine degradation, and argues that the presence of residual monomers does not create an oxidative environment. The first point is addressed in a subsequent section. As for the second point, Dr. Sessler explained that residual monomers, by themselves, cannot lead to oxidative degradation. (Tr. 457:3-8). He did admit, however, that residual monomers are an "easy-to-detect" surrogate for the corresponding monomer radical. (*Id.* at 526:9-15). In order for residual monomers to form monomer radicals and cause oxidative degradation, "[t]hey would have to react[, f]or instance, with peroxides, with activated forms of oxygen." (*Id.* at 458:10-23). As discussed above, peroxides are present in Watson's ANDA product. The presence of residual monomers working in tandem with other impurities such as peroxides creates an oxidative environment.

Novartis also alleges that polymerization initiators are present in Watson's ANDA product. Polymerization initiators are used in the manufacture of polymers, such as the 900A adhesive, and are capable of creating an oxidative environment. (JTX 23, p. 1; Tr. 421:7-19). According to Novartis, the "3M Patent Application shows that, in the absence of washing, residual initiator carries through to the final patches." (D.I. 322, p. 10; *see also* JTX 17, p. 7 ("Such polymerization reactions result in the formation of a polymer along with some level of unreacted monomers and initiator.")). This argument is not persuasive.[11] Unlike the residual monomers, the 900A specification does not say anything about residual polymerization initiator (JTX 23, p. 1), and polymerization initiator is not listed as being present in the certificate of analysis for the 900A adhesive. (JTX 186, p. 2644; JTX 30, p. 279745). Additionally, Novartis

[11] Novartis also cites an email from a Henkel employee stating that the 900A adhesive contains residual peroxide initiator as proof that TAPP is a component in Watson's ANDA product. (JTX 32, p. 285088; D.I. 322, p. 8). The Court relied on this email when Novartis cited it to show the presence of peroxides because there was other scientific evidence to corroborate that position. Here, aside from expert testimony and analogies based on other adhesive systems, the email is the only offered proof Novartis has that Watson's ANDA product contains residual initiator. It is also worth noting that TAPP is listed in the 900A specification as a monomer scavenger, not an initiator. (JTX 23, p. 1).

did not conduct any testing on the adhesives for Watson's ANDA product to establish the initiator's presence. It is possible an incomplete polymerization reaction in the 900A polymer left behind unreacted initiator, as Dr. Klibanov maintained (Tr. 179:19-181:20), but more concrete evidence is required to support that proposition. Reliance by analogy on a different patent application with a different adhesive is insufficient to prove that initiator in the 900A polymer adhesive carries over to the finished Watson ANDA product.

In sum, an oxidizing environment can be created by the presence of oxygen, peroxides, or other free radical generators. In this case, all three types of free radical generators can be found in Watson's ANDA products. Ambient air is not excluded from the manufacturing environment for Watson's ANDA products and was found to be present inside Watson's pouches. Dr. Davies tested the 900A and 905A adhesives and found peroxides, which Dr. Klibanov explained would be carried forward into Watson's ANDA product because no steps were taken to remove these impurities. Similarly, the documentation provided by Henkel shows that residual monomers are present in the 900A adhesive and are not removed prior to the assembly of Watson's ANDA product. The presence of these three free radical generators constitutes sufficient proof that Watson's ANDA product is an oxidizing environment.

b. Rivastigmine is susceptible to oxidative degradation in an oxidative environment

There is no dispute that rivastigmine is susceptible to degradation depending on the particular environment to which it is exposed. (Tr. 522:23-523:3). As discussed above, the environment for Watson's ANDA product contains oxygen, peroxides, and residual monomers. The question becomes whether these substances can oxidatively degrade rivastigmine. The answer to that question is yes, based on the evidence Novartis put forth regarding the individual

and collective effects of oxygen, peroxides, and residual monomers on rivastigmine. Each free radical generator's effect on rivastigmine will be discussed in turn.

Rivastigmine oxidatively degrades in the presence of oxygen. The patents in suit teach that rivastigmine in a transdermal device will degrade if exposed to oxygen despite "the formation of an occlusive polymer matrix around compound A [rivastigmine] and its storage in air-tight packaging." '031 patent, 1:22-28 ("It has now been found after exhaustive testing that compound A is susceptible to degradation, particularly in the presence of oxygen."). Novartis's experiments also showed that oxygen caused degradation to rivastigmine in its bulk form. (JTX 85, p. 2403 ("Rivastigmine base as liquid is very sensitive to oxygen (air) and moisture. Degradation is accelerated by the influence of heat.")). Indeed, Watson's own documents acknowledge oxygen's effects on rivastigmine. (JTX 29, p. 29808 ("Rivastigmine is subject to both hydrolytic and oxidative degradation.")).

Watson relies on a two-prong argument articulated by Dr. Sessler: "[F]or oxidative degradation to occur, oxygen must have both the 'power' to oxidize rivastigmine and must be present in a sufficient 'amount.'" (D.I. 318, p. 15). With respect to the first point, Dr. Sessler explained that molecular oxygen alone is insufficient to oxidatively degrade rivastigmine; instead, oxygen must react with another substance, such as a metal ion, to form a reactive oxygen species. (Tr. 443:1-23; *id.* at 420:1-24). Watson alleges that Novartis's failure to test for these other substances results in a failure to prove oxidative power. (D.I. 318, p. 15). Second, the amount of oxygen is important because of its role in the oxidation. Oxygen is not just an initiator; it is consumed in the reaction and incorporated into the ketone degradation product. Watson claims to use pressurized nitrogen gas to extrude the adhesives and a roller to squeeze all

of the air from its pouches prior to sealing,[12] both of which protect its ANDA product from oxygen. (*Id.*, p. 16). Therefore, the argument goes, "[w]ithout knowing the amount of oxygen, if any, in the adhesive system of the patch itself, it is impossible to determine whether enough oxygen is present to form the rivastigmine degradants." (*Id.*).

Dr. Sessler's concerns about oxygen's power to oxidize rivastigmine are overstated. Regardless of whether oxygen is labeled as a "strong" or "weak" oxidant in the organic environment, the need to protect the active substance in a transdermal patch from oxygen is well documented in the literature. ('031 patent, 1:22-28; '498 patent, 1:44-47 ("[T]he stability of the active substance and of the auxiliaries may be put at risk by reaction with active oxygen. Such active oxygen is, naturally, the oxygen of the air."); JTX 9, p. 110 (recognizing that oxidation may "occur spontaneously under the initial influence of atmospheric oxygen"); JTX 188, p. 1507). Even if oxygen is a relatively weak oxidant, as Dr. Sessler testified (Tr. 443:7-23 ("I've seen no evidence that under the normal conditions of Watson's ANDA product, manufacture, storage, transport, [and] use, that oxygen is even capable of triggering oxidative degradation. . . . Oxygen-based oxidation becomes weaker in an organic environment.")), he also conceded that peroxides and residual monomer radicals, in addition to metal ions, can create activated oxygen that would have the power to degrade rivastigmine. (*Id.* at 419:13-420:24 ("I think for oxygen to do its oxidative degradation, it has to be converted to some sort of active form. . . . Residual radicals left over perhaps from the polymerization process can trigger that kind of activation. Peroxides, as we've discussed, can either induce that kind of activation or act as an oxidant on their own.")). The presence of both peroxides and residual monomers leaves little doubt that

[12] The Court agrees with Novartis that it could not find any reference to a roller that squeezes air from the pouches in the cited portions of Watson's ANDA. (D.I. 318, p. 16; D.I. 322, p. 5; JTX 56, pp. 1830, 1834).

oxygen has the power required to oxidize rivastigmine in the environment of Watson's ANDA product.

Watson's second argument also misses the mark because the steps Watson took to eliminate air from its ANDA product were verifiably ineffective. There was a large enough volume of gas inside Watson's pouch to form a visible bubble when Dr. Davies rolled up the patch. (*Id.* at 340:15-341:21). Dr. Davies tested this gas with an oxygen meter and found the presence of oxygen in a concentration similar to that of ambient air. (JTX 54, p. 2; Tr. 340:8-14). It is highly probable the oxygen in the pouch will enter Watson's ANDA product because the patch was designed to be breathable. (Tr. 522:13-22). This is affirmed by Watson's acceleration lifetime studies, which prove that the amount of oxygen in the pouch is sufficient to oxidize rivastigmine because the ketone degradant is detected after 12 weeks of storage under normal conditions.[13] (JTX 195, p. 78375 (noting presence of ketone degradant at every time point from 12 weeks to 78 weeks under normal storage conditions)). When "stressed" conditions were applied, the ketone degradant appeared after just 4 weeks. (*Id.*).

Peroxides are also capable of oxidatively degrading rivastigmine, but most likely not at the levels measured by Dr. Davies. In order to reduce oxidative degradation, the '498 patent teaches that "an upper peroxide number limit of 20, better still 10, preferably 5, should not be exceeded." '498 patent, 7:16-17. Dr. Davies measured peroxide values of less than 2 in Watson's ANDA product (JTX 53, p. 2), which is well within what Watson describes as the "safe zone" taught by the '498 patent. (D.I. 318, p. 19). Novartis responds by pointing to a

[13] Given that the amount of ketone degradant detected in Watson's stability studies is unchanged over time within the limits of measurement precision, Watson suggests it could be due to the introduction of a trace impurity prior to the formation of the ANDA product. (D.I. 318, p. 23 n.14). This argument is unavailing in light of the weight of direct and circumstantial evidence proffered by Novartis.

different section of the '498 patent's specification that states "[a]n additional improvement in stability may be achieved by the addition of antioxidants," even if "the materials are virtually free from peroxides." '498 patent, 7:8-12. Given the diverging opinions from two highly qualified experts (*Compare* Tr. 189:23-190:13, *with* Tr. 429:22-430:21), this issue turns on their respective credibility as evaluated during the trial. The Court finds the teachings of the '498 patent and Dr. Sessler's trial testimony to be more persuasive. The low level of peroxides is unlikely to oxidatively degrade rivastigmine.

The fact that the peroxides, by themselves, likely are not present in sufficient quantities to cause oxidative degradation does not end the inquiry. As Dr. Klibanov noted, all three of the free radical generators discussed can create an oxidative environment that will lead to the oxidative degradation of rivastigmine. (Tr. 189:23-190:13). Peroxides can also react with oxygen and residual monomers to form activated oxygen and monomer radicals, both of which can also degrade rivastigmine. The low level of peroxides, therefore, does not alter the Court's view that rivastigmine is susceptible to degradation in Watson's ANDA product.

Finally, residual monomers, when present with other impurities known to exist in Watson's ANDA product, have the power to oxidize rivastigmine. Dr. Sessler stated this himself. (Tr. 458:10-23). As shown above, residual monomers are present in the 900A adhesive and also in Watson's ANDA product. Watson responds by arguing that the concentration of residual monomers is not sufficient to cause oxidative degradation. (D.I. 318, pp. 21-22). The 3M patent application, relied on by both parties, states, "The polymerization reaction product is washed such that the at least two ethylenically unsaturated monomers, if present in the adhesive as unreacted monomers after washing, are reduce[d] to a level of less than 200 ppm of total unreacted monomer, based upon the total weight of the adhesive." (JTX 17, p. 6). The 900A

adhesive, which contained 388 and 606 ppm residual monomers in the two certificates of analysis (JTX 186, p. 2644; JTX 30, p. 279745), represents only 34.7% of the total weight of the adhesive. (JTX 56, p. 1823). When the residual monomer concentration is adjusted based on the weight of the total adhesive, as taught in the 3M patent application, the resulting concentrations in the adhesive bilayer are 134 and 210 ppm, respectively.[14] (D.I. 318, p. 22). Watson contends that there is no oxidative environment because one value is substantially below the 200 ppm goal for washed adhesives taught by the 3M patent application, and the other value is only marginally above it. (*Id.*).

It is true that the 3M patent application suggests it is desirable to achieve less than 200 ppm of residual monomer by washing the polymerization reaction product. (JTX 17, p. 6). Although it recognizes that some embodiments may be stable after the washing process without the need to add an antioxidant, other embodiments will simply require a lesser amount of antioxidant to attain stability. (*Id.*). The need for an antioxidant is demonstrated by 3M's own experiments showing 0.95% oxidative degradation of rivastigmine occurred after two months at 60°C in a copolymer with no antioxidant, despite having a residual monomer concentration below the detection limit. (*Id.*, pp. 20-22; D.I. 322, pp. 9-10). Although the parties disagree on whether the level of residual monomers in Watson's ANDA product is sufficient to oxidatively degrade rivastigmine, the Court finds Novartis's position to be more credible.

It is clear that rivastigmine is subject to oxidative degradation in the presence of oxygen, peroxides, and residual monomers. It is also clear that each of these three free radical sources

[14] The concentrations of residual monomer in the adhesive bilayer were obtained by multiplying 34.7% by the residual monomer concentration in the 900A adhesive. This appears to assume that there are no residual monomers in the 905A adhesive, and, for purposes of this argument, the Court follows that assumption.

are present in Watson's ANDA products. This leads to the conclusion that Watson's ANDA products contain an environment in which one would expect rivastigmine to oxidatively degrade.

c. Rivastigmine does not significantly degrade in Watson's ANDA product and the most likely explanation is that BHT acts as an antioxidant

Watson's ANDA states that its products exhibit only a "low level of impurities and degradation products" when subjected to stress tests designed to predict degradation over a prolonged period of time. (JTX 56, p. 1826; Tr. 698:24-699:9). Based on its choices of excipients, Watson expected its ANDA product to maintain stability throughout the intended shelf life. (*Id.*). Watson's ANDA product also contains BHT. Dr. Kibbe, Watson's obviousness expert, admitted that the concentration of BHT claimed in the patents, and present in Watson's ANDA products, falls within what is "typically used in most pharmaceutical formulations." (Tr. 629:11-24; *see also* DTX 11, p. 47 (listing typical BHT concentrations for various uses)). This belies Watson's contention that "Plaintiffs have not presented any evidence that the small amounts of BHT at the levels detected by Dr. Davies could reduce oxidative degradation of rivastigmine in any formulation, much less in the environment of Watson's ANDA product." (D.I. 318, pp. 6-7). Dr. Klibanov offered the following explanation for the low level of degradation:

> Well, I think that one of skill in the art looking at this question will say [] we have rivastigmine, which is undeniably susceptible to oxidative degradation. You also have all this oxidative environment within Watson's adhesive bilayer. We have oxygen. We have peroxide[s]. We have residual initiators and monomers. And it's been shown that each one of those can lead to oxidative degradation [] of rivastigmine. And nevertheless, there is no significant oxidation of rivastigmine for a prolonged period of time. So one of skill in the art would look at that data and say, What is the most likely explanation for that? And [the] most likely explanation for that is that the BHT, which is undeniably present in the products affords significant stabilization for rivastigmine.

(Tr. 197:10-198:5).[15]

Watson criticizes Dr. Klibanov's analysis for incorrectly assuming that using an antioxidant and excluding oxygen are the only ways to prevent oxidative degradation in a transdermal product. (D.I. 318, p. 24). For example, Watson points to the '498 patent as evidence that the risk of oxidative degradation can be avoided by keeping the peroxide value number below 20—the peroxide value numbers measured by Dr. Davies in the 900A and 905A adhesives were less than 2. (*Id.*; '498 patent, 7:14-17). The '498 patent, however, addresses only oxidative degradation caused by peroxides. Residual monomers are not discussed, and excluding oxygen is suggested by the '498 patent. '498 patent, 1:44-50. Watson's argument would be more compelling if its ANDA product contained only peroxides. The facts of this case, however, are quite different, and Watson's ANDA product has been proven to contain both oxygen and residual monomers in addition to peroxides. Therefore, the teachings of the '498 patent are not directly on point and cannot support the broad assertion advanced by Watson that, independent of other impurities, a peroxide value number of less than 20 means oxidative degradation will be avoided.

Watson relies on the patents in suit for the proposition that trace amounts of free radicals will not negatively affect rivastigmine's stability. '031 patent, 1:44-46 ("The diluent or carrier may contain trace amounts of free radicals without affecting the stability of the pharmaceutical

[15] Novartis attempts to bolster Dr. Klibanov's opinion with Watson's experimental data on a prototype adhesive, the 9301 adhesive. (D.I. 310, p. 20). Watson conducted a stability test on the 9301 adhesive and found the degradation of rivastigmine without BHT to be significantly higher than the degradation of rivastigmine with BHT after 67 weeks. (JTX 205, pp. 25917-18 (finding addition of BHT resulted in between three and five fold decrease in rivastigmine degradation at both 25 and 40 degrees Celsius)). Watson decided not to pursue the 9301 adhesive, and it is not used in Watson's ANDA product. (Tr. 203:3-9). The 9301 adhesive is a very different formulation than the 900A and 905A adhesives: it uses a different polymerization initiator at a different concentration (*Compare* JTX 32, p. 285091, *with* JTX 23, p. 1), and contains vastly different concentrations of BHT. (*Compare* JTX 205 p. 25917, *with* JTX 41, p. 2). These experiments are certainly relevant in the sense that they demonstrate BHT's effect on rivastigmine degradation in the 9301 adhesive. The relevance to Watson's ANDA product and this case, however, is minimal given the number of differences between the adhesives and their constituent components.

composition."). It follows, according to Watson, that "the presence of some amount of free radicals in a transdermal system does not necessarily lead to an oxidative degradation problem." (D.I. 318, p. 24). The Court disagrees. The patents in suit contain an antioxidant, which assists in preventing oxidative degradation. It is more reasonable to conclude that the antioxidant shields rivastigmine from the free radicals' harmful effects than to conclude that free radicals do not create an oxidative environment. *See* '031 patent, 1:34-36.

Watson also asserts that Novartis should have performed additional testing. (D.I. 318, pp. 27-30). This argument is unavailing. The testing and other experimental data Novartis presented are sufficient to prove infringement by a preponderance of the evidence.

Watson's final argument is that Dr. Sessler's "footprint" hypothesis disproves Novartis's theory that BHT is acting as an antioxidant in Watson's ANDA product. Dr. Sessler posits that an antioxidant leaves a characteristic "footprint" involving the ratio of the degradants. According to the theory, rivastigmine degradation results in two main degradants, a styrene degradant and a ketone degradant, in approximately a 1:1 ratio. The styrene degradant forms first, and it can subsequently be oxidized to form the ketone degradant if an oxygen atom source is present. Unlike the styrene degradant, which can be formed via a non-oxidative pathway, the ketone degradant can only be formed through oxidation and consumes an oxygen atom in the process. The presence of an antioxidant will disrupt the oxidation reaction, blocking the ketone degradant's formation in the process. Therefore, the theory predicts the presence of a functioning antioxidant will result in more styrene degradant relative to the ketone degradant. (D.I. 318, p. 25 (citing various portions of Dr. Sessler's trial testimony)).

No experimentation was done to validate the theory,[16] but at trial both parties tested the theory's predictions by applying it to existing data. Watson supported its theory with a Novartis stability study on its transdermal device that found more ketone degradant than styrene degradant when no antioxidant was present, but more styrene degradant than ketone degradant when various antioxidants were added. (JTX 187, p. 504460). Novartis pointed to its stress tests on bulk rivastigmine, with no antioxidant present, which did not display the expected 1:1 ratio. The temperature and relative humidity were varied in the four experiments, and only one of the four demonstrated a 1:1 ratio. (JTX 85, p. 2399). In another Novartis test applying forced conditions to bulk rivastigmine, researchers observed a ketone to styrene ratio of nearly two-to-one. (*Id.*, p. 2401). Dr. Sessler attempted to fit this inconsistency into his theory by hypothesizing that oxygen is not a limiting reactant for bulk rivastigmine, but is limiting in a polymeric formulation. (Tr. 491:10-492:14 (citing JTX 195, p. 78375)). If that were the case, more of the ketone degradant would form with bulk rivastigmine because of the excess oxygen. (*Id.*). Although further experimentation may verify Dr. Sessler's theory in due course, the scientific evidence supporting the theory at this juncture is not robust enough for the Court to place its full faith in it.

Even if the "footprint" theory holds, however, its application to Watson's long-term stability test appears to be consistent with the presence of an antioxidant. The presence of an antioxidant, according to the theory, will result in a greater amount of styrene degradant than ketone degradant. In long-term stability testing done on Watson's ANDA product, the styrene and ketone degradant appeared in a 3:2 ratio. (JTX 195, p. 78375 (measuring approximately 0.03% styrene to 0.02% ketone by weight at time points between 26 and 78 weeks)). This is

[16] The exact rivastigmine degradation pathway underpinning the theory has not been scientifically established. (Tr. 556:13-23). Dr. Sessler himself described it as a "wonderful research study" that he did not conduct. (*Id.*).

entirely consistent with Novartis's contention that Watson's ANDA product contains an acting antioxidant, namely BHT. Dr. Sessler viewed this study's results differently, contending that the reported weight percentages were at the limits of precision. (Tr. 490:5-24). Because the numbers were so small, Dr. Sessler concluded the ratio at each time point was essentially 1:1 and that no antioxidant was present in the system. (*Id.* at 490:5-491:4). Without knowing the margin of error in the measurements it is impossible to tell with statistical certainty whether a ratio of 0.03:0.02 is really a 1:1 ratio. But three data points taken after 78 weeks were measured out to the thousandths decimal place and resulted in ratios of 0.029:0.021, 0.030:0.019, and 0.030:0.021. (JTX 195, p. 78375). All three figures after the decimal point are significant in each of those measurements, making it more likely that it is a 3:2 ratio. At the very least, based on the number of significant figures, the Court is not convinced they represent 1:1 ratios, as Dr. Sessler urges.

In sum, the Court reaches the same logical conclusion as Dr. Klibanov did. Rivastigmine, which is susceptible to oxidative degradation, and BHT, an antioxidant, are placed in a demonstrably oxidative environment, yet no significant degradation is observed over a prolonged period of time. The most likely explanation, and an explanation that Novartis has proven by a preponderance of the evidence, is that BHT is acting as an antioxidant to protect rivastigmine from oxidative degradation over a prolonged period of time.

II. OBVIOUSNESS

Watson asserts claims 2 and 7 of the '023 patent and claims 3, 7, 13, 16, and 18 of the '031 patent are invalid because the addition of an antioxidant to a rivastigmine transdermal patch would have been obvious to a person having ordinary skill in the art ("PHOSITA") in January 1998—the priority date. (D.I. 311, pp. 2-5; Tr. 34:6-8). This argument is premised on three

major pieces of prior art. The first piece of prior art is a British patent application, GB 2 203 040 A ("GB '040"), which was filed in 1988. GB '040 discloses rivastigmine's use in treating Alzheimer's disease and suggests a weight percent range of rivastigmine that would be effective in a transdermal device. (JTX 97, pp. 281395-97, 281408-11). The only limitation of the '023 and '031 patents' asserted claims not disclosed by GB '040 is the addition of an antioxidant. The second prior art reference is U.S. Patent No. 4,948,807 ("the '807 patent"), which issued in 1990. The purpose of the '807 patent is to identify alternatives to physostigmine, an acetylcholinesterase inhibitor used in the treatment of Alzheimer's disease that had several disadvantages, including chemical instability. '807 patent, 3:37-48. The '807 patent teaches that sterile injectable formulations of the "compounds of the invention," including the racemate RA_7, can incorporate an antioxidant. *Id.*, 7:15-53. The third piece of prior art is a scientific paper written in 1991 by Elmalem *et al.* The Elmalem article compared the effects of three new anti-acetylcholinesterase agents, one of which was RA_7, with that of physostigmine. (JTX 159, p. 1059). The "Methods" section described the preparation of the drugs in a saline solution with metabisulphite, a known antioxidant. (*Id.*, p. 1060).

Novartis counters that Watson failed to show by clear and convincing evidence that: a PHOSITA would have chosen GB '040's rivastigmine transdermal formulation as a starting point, rivastigmine was known in the art to be susceptible to oxidative degradation, and the use of an antioxidant would have been a predictable solution to rivastigmine's oxidative degradation problem. (D.I. 317, p. 7).

The obviousness inquiry must be conducted from the PHOSITA's point of view. The parties agree the PHOSITA has an advanced degree in pharmaceutics, chemistry, pharmaceutical chemistry, materials engineering, or the like, and at least two years of experience developing

pharmaceutical formulations. A PHOSITA could also possess a Bachelor's or Master's degree, provided the PHOSITA has practical experience working in the industry, or academia, for a longer period of time. (Tr. 589:1-590:3; *id.* at 817:13-818:21).

A. Legal Standard

The presumption that all patents are valid is the starting point for any obviousness determination. 35 U.S.C. § 282 (2012). Under § 103(a), a patent "may not be obtained . . . if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art." *Id.* § 103(a). Obviousness is a question of law that depends on the following factual inquiries: (1) the scope and content of the prior art; (2) the differences between the claims and the prior art; (3) the level of ordinary skill in the relevant art; and (4) any objective considerations such as commercial success, long felt but unsolved need, and the failure of others. *See Transocean Offshore Deepwater Drilling, Inc. v. Maersk Drilling USA, Inc.*, 699 F.3d 1340, 1347 (Fed. Cir. 2012). The improvement over the prior art must be "more than the predictable use of prior art elements according to their established functions." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 417 (2007).

To prove obviousness, Watson must show that a PHOSITA would be motivated to combine the claimed combinations with a reasonable expectation of success. *Allergan, Inc. v. Sandoz Inc.*, 726 F.3d 1286, 1291 (Fed. Cir. 2013). Evidence of obviousness, especially when that evidence is proffered in support of an "obvious-to-try" theory, is insufficient unless it indicates that the possible options skilled artisans would have encountered were "finite," "small," or "easily traversed," and "that skilled artisans would have had a reason to select the route that produced the claimed invention." *In re Cyclobenzaprine Hydrochloride Extended-Release*

Capsule Patent Litig., 676 F.3d 1063, 1072 (Fed. Cir. 2012). Obviousness must be proven by clear and convincing evidence. *Id.* at 1078.

B. Findings of Fact

1. GB '040, the '807 patent, and the Elmalem article are all prior art.
2. The use of rivastigmine in a transdermal patch to treat Alzheimer's disease was known.
3. Rivastigmine was not known to be susceptible to oxidative degradation.
4. Neither the '807 patent nor the Elmalem article teach a PHOSITA that rivastigmine is susceptible to oxidative degradation.
5. It would not have been obvious to a PHOSITA to combine an antioxidant with rivastigmine in a transdermal patch.

C. Conclusions of Law

Watson contends a PHOSITA would have been motivated to develop a rivastigmine transdermal patch based on the teachings of GB '040, the closest piece of prior art to the patents in suit. GB '040 documents rivastigmine's efficacy in the treatment of Alzheimer's disease, and discloses therapeutic benefits that can be obtained through the use of a transdermal formulation. The '807 patent and the Elmalem article disclose the combination of RA_7[17] with an antioxidant, which teaches a PHOSITA that RA_7 is susceptible to oxidative degradation and recognizes the addition of an antioxidant as a solution to the problem. Therefore, Watson contends, a PHOSITA seeking to improve upon the rivastigmine transdermal device of GB '040, or any other rivastigmine formulation, would have conducted routine stability testing and would have been motivated to add an antioxidant if any oxidative degradation were identified.

[17] Dr. Klibanov agrees the stability of RA_7 and rivastigmine is identical. (Tr. 896:2-5 ("[T]he Court will remember that stability toward oxidative degradation of rivastigmine[] and RA_7 is the same, and it's not a controversial issue.")).

This argument is a logical one, but it overstates the teachings contained in these prior art references. Neither the '807 patent nor the Elmalem article teach a PHOSITA that rivastigmine is susceptible to oxidative degradation. These references certainly disclose that an antioxidant *can* be added to RA_7, but there is no accompanying suggestion that RA_7 is susceptible to oxidative degradation or that an antioxidant is needed. Without a motivation to add an antioxidant to the rivastigmine transdermal device disclosed in GB '040, Watson's obviousness case falls short.

1. GB '040

As discussed briefly above, GB '040 discloses many limitations of the claims at issue. It discusses both the free base and acid addition salt forms of rivastigmine (JTX 97, pp. 281396-97) and recognizes rivastigmine's ability for "marked and selective inhibition of the acetylcholinesterase" (*id.*, p. 281397), which makes it useful for the treatment of Alzheimer's disease. (*Id.*, p. 281395). GB '040 also acknowledges some advantageous aspects of transdermal delivery[18] with respect to drug tolerability including "long-lasting and constant inhibition of acetylcholinesterase activity" and a "slow onset of action." (*Id.*, p. 281408). Finally, GB '040 discloses a therapeutically effective dose of rivastigmine, for example "about 1 to about 20 % by weight of active agent" (*id.*, p. 281411), which falls within the range of the asserted claims, and it discusses the use of a diluent or carrier. (*Id.*). Both parties' experts agree GB '040 did not disclose or otherwise suggest that rivastigmine, in any formulation, was susceptible to oxidative degradation. (Tr. 710:16-711:5; *id.* at 834:16-24).

[18] Although GB '040 highlights several benefits of transdermal formulations, that cannot be fairly characterized as the patent application's main purpose. The virtues of other formulation methods were also discussed (JTX 97, p. 281398), and the central innovation of GB '040 is the "surprising[]" and "unexpected" discovery of rivastigmine's selective inhibition of acetylcholinesterase. (*Id.*, p. 281397).

A PHOSITA would not have been motivated to include an antioxidant in any formulation unless there was evidence of oxidative degradation. Excipients, including antioxidants, are inactive ingredients of a pharmaceutical composition that are added to ensure the drug performs its function in a desirable fashion. (*Id.* at 836:22-837:18). The excipients themselves offer no therapeutic benefit. (*Id.* at 837:11-18). In fact, excipients can be incompatible with the drug or other excipients in the pharmaceutical composition, which could lead to a deleterious effect on the drug's performance. (*Id.* at 838:22-840:12 (quoting JTX 188, p. 1507)). The compatibility of an excipient with a given pharmaceutical composition cannot be predicted without experimentation because of the numerous possible chemical reactions. (*Id.* at 841:21-842:3). For this reason, the European Agency for the Evaluation of Medicinal Products—the FDA's European equivalent—instructed, "Antioxidants should only be included in a formulation if it has been proved that their use cannot be avoided." (JTX 105, p. 2).

Moreover, oxidative degradation is not the only degradation pathway; there were many known types of degradation at the time of the invention. These include hydrolysis, reduction, racemization, photolysis, and pyrolysis. (Tr. 812:10-17; *id.* at 825:21-826:9). But not every drug in every formulation is susceptible to all types of degradation, and, due to the risk of incompatibility discussed above, a PHOSITA would not have added an excipient to prevent each of these types of degradation. A PHOSITA would only be motivated to address and correct known degradation problems. (*Id.* at 811:19-812:9). Because GB '040 was silent with respect to rivastigmine's instability, this motivation would have had to come from some other prior art reference.

2. The '807 Patent

Although the '807 patent does disclose the addition of an antioxidant to RA_7, it does not teach a PHOSITA that RA_7 oxidatively degrades. The purpose of the '807 patent is to identify alternatives to physostigmine, an anti-acetylcholinesterase that lacked the desired chemical stability. '807 patent, 3:37-39. The patent discloses a general formula for a large number of phenyl carbamate compounds—in excess of 8 million (Tr. 847:23-848:16)—several of which were selected for further testing, including RA_7. '807 patent, 4:21-53; *id.*, tbls. 1-3. RA_7 is one of the compounds identified and later claimed by the '807 patent. The '807 patent discusses the use of RA_7 in tablets, capsules, and elixirs for oral administration, as well as sterile solutions and suspensions for parenteral administration. *Id.*, 7:15-19. Among the "adjuvants" that can be used with tablets and capsules are: binders, excipients, disintegrating agents, lubricants, sweetening agents, and flavoring agents. *Id.*, 7:27-35. The patent provides similar, shorter lists of adjuvants for capsules and elixirs. *Id.*, 7:35-44. For sterile compositions, however, the '807 patents states, "Buffers, preservatives, antioxidants and the like can be incorporated as required." *Id.*, 7:45-50. The patent then lists several preferred antioxidants.

At first glance, this statement appears to support the proposition for which Watson cited it: namely, that it teaches a PHOSITA that RA_7 is susceptible to oxidative degradation and needs an antioxidant to maintain stability. But despite the laundry list of compounds that "can be incorporated," there is no specific example in the '807 patent combining RA_7 with an antioxidant. (Tr. 719:16-720:14). Moreover, the '807 patent disclosed the addition of an antioxidant "as required," yet nothing in the '807 patent suggests RA_7 requires an antioxidant (*id.* at 718:20-719:15; *id.* at 861:5-862:3), and there is no discussion of the appropriate amount of antioxidant, if required, that should be used for any of the compounds. (*Id.* at 862:6-13). There

is no mention of any observed oxidative degradation of RA_7, and the patent contains no stability data. (*Id.* at 715:24-716:22; *id.* at 863:2-24). To the extent stability is mentioned in the '807 patent, it portrays RA_7 and the other compounds of the invention in a positive light. *See* '807 patent, 11:26-35 (positing that the superior *in vivo* potency of the compounds of the invention may be due to their greater chemical stability relative to physostigmine); *id.*, 3:37-39 (recognizing one of the patent's purposes as "provid[ing] new carbamate derivatives which show greater chemical stability than physostigmine"). Finally, it is worth noting that the patent examiner for the '023 and '031 patents considered both the '807 patent and U.S. Patent No. 5,602,176, which is the American equivalent of GB '040. (JTX 3, pp. 1063, 1083; JTX 4, p. 914; Tr. 830:4-831:14; *see also Sciele Pharma Inc. v. Lupin Ltd.*, 684 F.3d 1253, 1260 (Fed. Cir. 2012) (explaining that "whether a reference was before the PTO goes to the weight of the evidence," and "it may be harder to meet the clear and convincing burden when the invalidity contention is based upon the same argument on the same reference that the PTO already considered")). When reading this reference as a whole, it would not teach a PHOSITA that an antioxidant was required to protect rivastigmine from oxidative degradation.[19]

3. The Elmalem Article

The Elmalem article also fails to teach a PHOSITA of rivastigmine's susceptibility to oxidative degradation. Elmalem compares the effects of three phenyl carbamate compounds with physostigmine on the morphine-induced respiratory depression in rabbits. (JTX 159, p. 1059). One of the phenyl carbamate drugs tested was RA_7. The key sentence is found in the

[19] Unlike the other asserted claims, which Waston argues are obvious in light of GB '040 in combination with other prior art references, Watson asserts claim 16 of the '031 patent would be obvious in light of the '807 patent alone and claim 18 of the '031 patent would be obvious in light of the '807 patent and *The Handbook of Pharmaceutical Excipients*. Because the '807 patent does not teach a PHOSITA that rivastigmine is susceptible to oxidative degradation and requires the protection of an antioxidant to maintain stability, its statement that an antioxidant can be incorporated as required does not render the method in claims 16 or 18 of the '031 patent obvious.

"Methods" section of the paper, which states: "All drugs were made up freshly in sterile saline, which included an equal weight of sodium metabisulphite, to prevent oxidation." (*Id.*, p. 1060). To Watson, this unequivocally "taught one of ordinary skill that rivastigmine was susceptible to oxidative degradation and to add an antioxidant to the pharmaceutical composition to prevent it." (D.I. 311, p. 13).

Novartis's interpretation of this passage is more nuanced and decisively divergent. According to Dr. Klibanov, the Elmalem article reports the findings of a well-controlled experiment, *i.e.*, one in which any variability that can be eliminated is eliminated. The stated purpose of the Elmalem paper was to compare the effects of three new agents with that of physostigmine. (JTX 159, p. 1059). The simplest way to conduct this experiment would be to prepare aqueous solutions of these four compounds and compare their effects when injected into rabbits. (Tr. 887:20-888:5). The problem with this experiment's design is physostigmine's well-documented lack of stability in aqueous solution. ('807 patent, 1:32-34 ("[Physostigmine] is chemically unstable and must be prepared in solution with an antioxidant, and protected from light."); JTX 148, p. 1266 ("Physostigmine is not stable in aqueous solution."); JTX 159, p. 1059 (recognizing physostigmine's "low chemical stability" as a serious disadvantage); Tr. 888:6-9). The instability can be remedied by adding an antioxidant to the physostigmine solution. (Tr. 888:10-11). If, however, the experiment were conducted with physostigmine and an antioxidant injected into one rabbit, and the other three compounds, without an antioxidant, injected into three other rabbits, there would be no way to determine whether any observed difference in the rabbits' respiratory depression was attributable to the relative chemical activity of the drug or to the presence of the antioxidant. (*Id.* at 888:15-20). The authors of the Elmalem article addressed this concern by adding an antioxidant to all of the drug formulations, including the saline

placebo. (*Id.* at 889:5-14; *id.* at 891:6-11). When read in this context, the statement, "All drugs were made up freshly in sterile saline, which included an equal weight of sodium metabisulphite, to prevent oxidation," is better understood as a measure to reduce variability than a teaching that RA_7 is subject to oxidative degradation.[20] Indeed, the Elmalem paper did not disclose any stability data for RA_7. As such, the Elmalem paper would not have motivated a PHOSITA to combine an antioxidant with the transdermal rivastigmine device disclosed by GB '040.

Watson criticizes this "tortuous interpretation" of Elmalem as an attempt to avoid its plain teaching. (D.I. 323, pp. 10-11). First, Dr. Klibanov's reading of Elmalem requires both that saline be considered a drug and that an antioxidant be added to the saline as a control. (*Id.* at 10). Saline is not mentioned as a drug in the "Drugs" section of the paper, and it does not make sense that "[a]ll drugs were made up freshly in sterile saline" if the authors considered saline itself to be a drug. (JTX 159, p. 1060; D.I. 323, p. 10). The article summary in Elmalem, however, states, "Each drug, RA_6, (1 mg i.v., 2 mg s.c.) RA_7 (1 or 2 mg i.v.); RA_{15} (0.25 or 0.5 mg i.v.), physostigmine (0.05 or 0.1 mg i.v.) or saline (1 ml), was injected simultaneously with morphine (8 mg i.v.) to groups of 6-10 rabbits." (JTX 159, p. 1059 (punctuation as in original)). The Court accepts Novartis's argument that this passage indicates the study's use of the word "drugs" includes RA_6, RA_7, RA_{15}, physostigmine, and saline, with saline acting as a placebo. (Tr. 886:5-16). It is also logical to conclude that the Elmalem authors added an antioxidant to saline, even though it has no stability issues, because it reduces one of the variables in the experiment. (*Id.* at 888:10-889:2).

[20] Dr. Klibanov argues that the chemical structure of RA_7 and physostigmine bolsters his reading of Elmalem. Physostigmine is a monomethyl carbamate, whereas RA_7 is a dialkyl carbamate. (D.I. 317, p. 20). The former is unstable in aqueous solution, but the latter is not. (Tr. 879:21-882:21; JTX 147, p. 133; JTX 146, pp. 616-17). A PHOSITA reading Elmalem would appreciate the structural difference between the two drugs and would not have expected RA_7 to oxidatively degrade in aqueous solution. (Tr. 884:4-15). Therefore, the argument goes, it is more likely that the antioxidant was added as a control than to protect RA_7 from oxidative degradation.

Second, Watson contends that under Dr. Klibanov's interpretation, the methodology of Elmalem would not be reproducible because a PHOSITA would not know how much antioxidant to add to the saline solution. (D.I. 323, pp. 10-11). In fact, Dr. Klibanov testified that he did not know how much antioxidant was used in any of the formulations. (Tr. 933:6-12). To Dr. Kibbe, the sentence, "drugs were made up freshly in sterile saline, which included an equal weight of sodium metabisulphite," instructs a PHOSITA to add an amount of antioxidant to each drug formulation that is equivalent to the weight of the drug in that solution. (*Id.* at 664:13-665:13). This tells a PHOSITA how much antioxidant to add to each formulation, but it introduces a new variable because a different amount of antioxidant would be present in each of the injectable formulations.[21] (*Id.* at 891:15-892:10).

This second issue was hotly contested at trial. One seemingly innocuous sentence has given rise to diametrically opposed interpretations, neither of which is without its criticisms. There does not appear to be an objectively "correct" reading; rather both arguments seem logical and are supported by highly qualified experts in the field. Instead of attempting to explain scientifically why one explanation is superior to the other, the better method for resolving this dispute is based on credibility. To that end, the position advanced by Novartis better comports with the Court's understanding of Elmalem, and the Court credits Novartis's accompanying trial testimony as being more credible. Watson has not convinced the Court, by clear and convincing evidence, that Dr. Klibanov's view of the Elmalem article is incorrect. Therefore, the Court accepts Dr. Klibanov's argument on this point, and adopts it as the Court's finding of fact.

[21] The authors in Elmalem did not use the same concentration of each drug in the experiment.

4. Watson's Other Prior Art References

Watson also relies on U.S. Patent No. 5,580,572 ("the '572 patent") and *The Handbook of Pharmaceutical Excipients*, Second Edition (DTX 7) as prior art references that can be combined with GB '040 to invalidate several of the asserted claims. The '572 patent discloses a transdermal matrix system for delivering hormones. It teaches the inclusion of an antioxidant, within the concentration ranges claimed in the patents in suit, to stabilize the polymer matrix. ('572 patent, 4:47-52, 16:23; Tr. 648:18-649:18). According to Watson, this would have instructed a PHOSITA that antioxidants could be used to stabilize the polymer in a polymer matrix. (D.I. 311, p. 15). The '572 patent may indeed teach a PHOSITA that, but Watson has not shown any motivation for the PHOSITA to combine GB '040 with the '572 patent. When discussing the transdermal administration of rivastigmine, GB '040 specifically cites to the hydrophilic polymers described in European Patent Application 0 155 229 ("EP '229"). (JTX 97, p. 281411). The transdermal devices in EP '229 do not suggest using an antioxidant. (JTX 109; Tr. 734:17-22). Additionally, rivastigmine is not mentioned in the '572 patent, and the hormones in the '572 patent share no chemical or structural similarities with rivastigmine. (Tr. 733:5-11).

The *Handbook of Pharmaceutical Excipients* provides guidance on what antioxidants are suitable for inclusion in pharmaceutical compositions and suggests typical concentration ranges for each antioxidant. (Tr. 631:5-632:21; *see, e.g.*, DTX 7, p. 12). The *Handbook* discloses the antioxidants claimed in the patents in suit, in amounts that fall within the claimed concentration ranges. (Tr. 630:14-644:22). Watson asserts a PHOSITA seeking to add an antioxidant to a transdermal rivastigmine formulation would have referred to the *Handbook*. It is true that the *Handbook* discloses the antioxidants claimed, but absent a reason to believe an antioxidant was

required for a rivastigmine formulation, a PHOSITA would not be motivated to consult the *Handbook*. Because the Court has concluded that nothing in the prior art disclosed rivastigmine's susceptibility to oxidative degradation, a PHOSITA would have no reason to combine the *Handbook*'s teachings with any other prior art reference.

In conclusion, the obviousness determination in this case turns on whether a PHOSITA in January 1998, looking at all of the prior art, would have known rivastigmine was susceptible to oxidative degradation. If the answer is yes, the asserted claims of the '023 and '031 patents are invalid because the addition of an antioxidant to a pharmaceutical composition that oxidatively degrades is one of several known, obvious solutions. *See KSR*, 550 U.S. at 421 ("When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense."). If the answer is no, then the discovery that rivastigmine oxidatively degrades and the solution to that problem are an inventive contribution worthy of patent protection. There can be no motivation to combine prior art references to solve a problem that no one knows exists. *Id.* at 418 ("Although common sense directs one to look with care at a patent application that claims as innovation the combination of two known devices according to their established functions, it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does."). Because I find that a PHOSITA would not have appreciated rivastigmine's susceptibility to oxidative degradation in January 1998, Watson has not proven obviousness by clear and convincing evidence.

III. CONCLUSION

Novartis proved Watson's ANDA products infringe claims 2 and 7 of the '023 patent and claims 3, 7, 13, 16, and 18 of the '031 patent by a preponderance of the evidence. Watson failed to prove by clear and convincing evidence that any of the asserted claims of the '023 or '031 patents were invalid. Novartis should submit an agreed upon form of final judgment within two weeks.

US006335031B1

(12) **United States Patent**
Asmussen et al.

(10) **Patent No.: US 6,335,031 B1**
(45) **Date of Patent: Jan. 1, 2002**

(54) **TTS CONTAINING AN ANTIOXIDANT**

(75) Inventors: **Bodo Asmussen**, Bendorf-Sayn; **Michael Horstmann**, Neuwied, both of (DE); **Kai Köpke**, Triengen (CH); **Henricus L. G. M. Tiemessen**, Weil-Haltingen (DE); **Steven Minh Dinh**, Briarcliff Manor; **Paul M. Gargiulo**, New York, both of NY (US)

(73) Assignees: **Novartis AG**, Basel (CH); **LTS Lohmann Therapie-Systeme GmbH Co. KG**, Neuwied (DE)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/291,498**

(22) Filed: **Apr. 14, 1999**

Related U.S. Application Data

(63) Continuation-in-part of application No. PCT/EP99/00078, filed on Jan. 8, 1999.

(30) **Foreign Application Priority Data**

Jan. 12, 1998 (DE) 9800526

(51) **Int. Cl.**[7] **A61F 13/00**

(52) **U.S. Cl.** **424/449**; 424/448; 602/57; 602/60; 604/290; 604/305; 604/307

(58) **Field of Search** 424/449, 448; 602/57, 60; 604/290, 305, 307

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(57) **ABSTRACT**

Pharmaceutical composition comprising (S)-N-ethyl-3-[1-dimethylamino)ethyl]-N-methyl-phenyl-carbamate in free base or acid addition salt form and an anti-oxidant. Said pharmaceutical compositions may be delivered to a patient using a transdermal delivery device.

20 Claims, No Drawings

EXHIBIT 38
Deponent Buckton
Date 5/8/13 Rptr.
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Novartis Pharmaceuticals Corp., et al. v. Par Pharmaceutical, Inc., et al.
JTX001

TTS CONTAINING AN ANTIOXIDANT

This a continuation-in-part of application PCT/EP99/00078, filed Jan. 8, 1999. The entire contents of the PCT/EP99/00078 disclosure are incorporated herein by reference.

This invention relates to a pharmaceutical composition for systemic administration of a phenyl carbamate, e.g. by transdermal administration. In particular this invention relates to a pharmaceutical composition of the phenyl carbamate—(S)-N-ethyl-3-[1-dimethylamino)ethyl]-N-methyl-phenyl-carbamate—(hereinafter referred to as compound A) in free base or acid addition salt form as disclosed in published UK patent application GB 2 203 040, the contents of which are incorporated herein by reference.

Compound A is useful in inhibiting acetylcholinesterase in the central nervous system, e.g. for the treatment of Alzheimer's disease.

A transdermal composition in the form of a patch is described in Example 2 of GB 2,203,040 according to which compound A is mixed with two polymers and a plasticiser to form a viscous mass. This mass is applied to a foil which is cut into patches.

It has now been found after exhaustive testing that compound A is susceptible to degradation, particularly in the presence of oxygen. The transdermal composition described in GB 2203040 has been found to degrade, possibly by oxidative degradation, despite the formation of an occlusive polymer matrix around compound A and its storage in air-tight packaging.

The present applicant has found that stable pharmaceutical compositions comprising compound A can now be obtained, which show insignificant degradation of compound A over a prolonged time period, e.g. 2 years, as indicated by standard tests, e.g. stress tests.

In one aspect, the invention provides a pharmaceutical composition comprising Compound A in free base or acid addition salt form and an anti-oxidant.

The pharmaceutical compositions of the present invention show a reduction in degradation by-products in stress stability tests.

The pharmaceutical compositions of the invention may contain high amounts of compound A, e.g. from 1 to 40% by weight, e.g. 10–35%, more particularly 20–35%, e.g. 30%.

The compound A may be in any of a wide variety of pharmaceutical diluents and carriers known in the art. The diluent or carrier may contain trace amounts of free radicals without affecting the stability of the pharmaceutical composition of the invention.

The diluent or carrier is preferably one or more polymers, more preferably a hydrophilic polymer or polymers. In a preferred embodiment the diluent of carrier is selected from at least one polymer selected from acrylate polymers, and polymethacrylate polymers. The polymers preferably have a mean molecular weight of from about 50,000 to about 300,000 Daltons, e.g. 100,000 to 200,000 Daltons. The polymers preferably are capable of forming a film, thus to be compatible to the skin.

As a polymer one can mention in particular an acrylate co-polymer, e.g. co-polymers of butyl acrylate, ethyl hexyl acrylate and vinyl acetate. Preferably the polymer is cross-linked. A preferred acrylate polymer is one of the Durotak brand available from National Starch and Chemical Company, Zutphen, Holland, e.g. Durotak 87-2353 (hereinafter polymer A), 387-2051 or 387-2052 (hereinafter polymer D).

The diluent or carrier is preferably present in an amount of up to 90%, more preferably 70% by weight base on the total weight of the pharmaceutical composition.

The polymer, when a hydrophilic polymer, may conveniently take up water and is permeable to water, e.g. moisture from the skin, although the polymer may be insoluble in water. The polymer may swell and provide release of a large amount of pharmacologically active agent leading to a high concentration gradient of pharmacologically active agent between the skin surface and stratum comeum at a pH of from 4 to 7, preferably at skin pH, e.g. around 5.5. If desired such polymers may be soluble in organic solvents.

Examples of suitable polymers include polyacrylamide and its co-polymers, polyvinylpyrrolidone (PVP), vinyl acetate/vinyl alcohol co-polymers, polyvinyl alcohol (PVA) and derivatives, ethyl cellulose and other cellulose and starch derivatives.

Hydrophilic polyacrylates are preferred polymers. The polyacrylate may be substituted, e.g. a methacrylate. They may be commercially available acrylate/methacrylate co-polymers. Some or all of the acid groups may be esterified, e.g. with alkyl (C_{1-10}) groups, more particularly alkyl groups having 1 to 4 carbon atoms such as methyl or ethyl groups.

Examples of commercially available polymers of this type include:

1) Polymers of methacrylate containing alkyl (C_{1-4}) ester groups. Preferably the polymer matrix is a mixture of an acrylate polymer and a methacrylate polymer e.g. in a weight ratio of from 5:1 to 1:1, e.g. 4:1 to 2:1 e.g. 3:1, e.g. butylmethylacrylate and methylmethylacrylate. MW 20000, e.g. Plastoid B from Röhm, Darmstadt, Germany (hereinafter polymer B).
2) Polymers of acrylate and methacrylate esters containing methyl and ethyl neutral ester groups and trimethylaminoethyl cationic ester groups. Chloride ions may be present. Mean Molecular weight 150000 Daltons. Viscosity (20° C.), maximum 15 cP. Refractive index 1.380–1.385. Density 0.815–0.835 g/cm^3. Ratio of cationic ester groups to neutral alkyl groups 1:20 giving an alkali count of 28.1 mg KOH per gram polymer (Eudragit RL 100 Registered Trade Mark available from Röhm) or 1:40 giving an alkali count of 15.2 mg KOH per gram polymer (Eudragit RS 100 Registered Trade Mark, also available from Röhm).
3) Polymers of methacrylate esters containing trimethylaminoethyl cationic ester groups and other neutral (C_{1-4})alkyl ester groups. Chloride ions may be present. Mean molecular weight 150,000. Viscosity (20° C.) 10 cP. Refractive Index 1.38. Density 0.815. Alkali number of 180 mg KOH per gram polymer (Eudragit E 100, Registered Trade Mark, also available from Röhm and hereinafter referred to a polymer C).

If desired the pharmaceutical composition may contain other additives, such as plasticizers and/or softeners preferably skin compatible tensides, e.g. to provide flexibility to the pharmaceutical composition, and/or to dissolve partially or totally compound A.

Examples of additives include:

1) Polyoxyethylene fatty alcohol ethers. The alcohol may e.g. be a C_{12-18} alcohol. The HLB value may be e.g. from 10 to 18. A preferred example is polyoxyethylene-(10) oleyl ether. A suitable ether may have a viscosity (25° C.) of about 100 cP, a solidification point of about 16° C., an HLB value of 12.4 and an acid count maximum 1.0 (Brij 97 Registered Trade Mark available from Atlas Chemie, Germany).
2) Polyoxyethylene Sorbitan fatty acid esters. The fatty acid may be e.g. a C_{12-18} fatty acid. The HLB value may be e.g. from 10 to 18. A preferred example is polyoxyethylene-

(20) sorbitan monooleate, e.g. Tween 80, Registered Trade Mark available from Atlas Chemie, Germany.

3) Polyoxyethylene-(5-40) stearic acid esters, e.g. Myrj (Registered Trade Mark) available from Atlas Chemie, Germany.

4) Polyoxyethylene glycol fatty alcohol ethers, e.g. polyethylene glycol-(6-25) cetyl ether, glycerin polyethylene ricinoleate, glycerin polyethylene glycol stearate (Cremophor brand, Registered Trade Mark available from BASF Germany).

5) Polyoxyethylene glycols of MW from 200 to 600 Daltons, e.g. 300 or 400 Daltons.

6) Esters of poly(2-7)ethylene glycol glycerol ether having at least one hydroxyl group and an aliphatic (C_{6-22}) carboxylic acid, e.g. Polyethylene glycol-(7) glyceryl cocoate, e.g. Cetiol HE, Registered Trade Mark, from Henkel, Germany.

7) Adipic acid lower alkyl esters, e.g. di-n-butyl adipate and diisopropyl adipate.

8) Glycerin polyethylene glycol ricinoleate, e.g. Product of 35 moles ethylene oxide and castor oil, e.g. Brand Cremophor EL Registered Trade Mark, obtainable from BASF, Germany.

9) Tracetin-(1,2,3).

10) Fatty acid, e.g. a C_{12-18} fatty acid.

11) Fatty alcohol, e.g. a C_{12-18} fatty alcohol.

The amount and type of additive required may depend on a number of factors, e.g. the HLB value of the tenside and the flexibility of the pharmaceutical required. The amount of additive does not significantly influence the capability of the polyacrylate to form films. Generally the weight ratio of tenside to the polymer may be from about 1:10 to 5:1, e.g. 1:10 to 1:3.

Preferably, however, no such additive is present or is only present in an amount less than 1% by weight based on the total weight of the pharmaceutical composition.

The pharmaceutical composition may contain skin penetration promoters, e.g. 1-dodecylazacycloheptan-2-one (azone) and N,N-diethyl-m-toluamide (DEET).

The amount and type of skin penetration promoter, and/or additives present may depend on a number of factors. Generally the weight ratio of skin penetration promoting agent to hydrophilic polymer will be from about 1:1 to 1:10. Preferably the amount of tenside and/or skin penetration promoter may be from about 3 to about 50%, preferably 20 to 40% by weight of the pharmaceutical composition.

Preferably however no such additive is present or is only present in an amount less than 1% by weight of the pharmaceutical composition.

If desired the pharmaceutical composition may contain a hydrophobic elastomer, e.g. a synthetic resin. Such resins are conventional in the plaster art. Suitable resins may include non-swellable acrylate resins. These may if desired be adhesive. The weight ratio of polymer, e.g. hydrophilic polymer to resin may for example be from 1:0.5 to 1:10. The resin may contain modifiers, extenders, e.g. of softening point about 50 to 100° C. Such extenders may have adhesive or softening properties. Examples of such extenders may include resin acids, glyceryl and phthalate esters of resin acids.

A preferred pharmaceutical composition according to the invention comprises

a) (S)-N-ethyl-3-[1-dimethylamino)ethyl]-N-methyl-phenyl-carbamate as compound A in free base form in an amount of 20 to 40 weight-%,

b) polymethacrylate in an amount of 10 to 30% by weight

c) acrylate copolymer in an amount of 40 to 60% by weight, and

d) α-tocopherol in an amount of between 0.05 and 0.3% by weight

wherein the total weight of the pharmaceutical composition is 100%.

In another aspect the present invention provides the use of an anti-oxidant to stabilize a pharmaceutical composition containing Compound A.

Before the finding by the present applicant that an anti-oxidant is necessary in compositions of this invention, it was hitherto thought unnecessary.

The applicant has found that an effective stabilising effect is surprisingly achieved when the antioxidant is selected from tocopherol, esters thereof, e.g. tocopherol acetate, ascorbyl palmitate, ascorbic acid, butylhydroxytoluene, butylhydroxyanisole or propyl gallate, preferably α-tocopherol or ascorbyl palmitate. The antioxidant may be conveniently present in an amount of from about 0.01 to about 0.5%, e.g. 0.05 to 0.20, e.g. 0.15%, more particularly 0.1% by weight based on the total weight of the pharmaceutical composition.

Pharmaceutical compositions of the invention produced in analogous manner to example 1 described hereinafter containing 0.1% tocopherol show for Example only 1.3% degradation products compared to 4.46% degradation products in equivalent compositions not containing tocopherol in 2 month stress tests at 60° C. Pharmaceutical compositions of the invention in analogous manner to example 1 described hereinafter containing 0.15% tocopherol show for example only 0.25% degradation products compared to 1.09% degradation products in compositions not containing tocopherol in 3 month stress tests at 40° C. at 75% room humidity.

The pharmaceutical composition of the invention is preferably used for transdermal application.

In another aspect of the invention there is provided a transdermal device for administering a Compound A which comprises a pharmaceutical composition containing Compound A, a backing layer providing support for the pharmaceutical composition, an adhesive for fixing the pharmaceutical composition to the backing layer and a release-liner releasably contacting said adhesive.

The pharmaceutical composition may be conveniently contained in a discrete thin layer, the upper and lower surfaces of which may be coated in a layer of adhesive the surface of which in turn provide backing layer and release-liner contacting surfaces.

The pharmaceutical composition contained in the discrete layer may comprise the Compound A and other excipients in a polymer matrix, the polymer matrix therefor being provided by the diluent or carrier aforementioned. If desired Compound A may be dispersed throughout, or dissolved in, said polymer matrix.

The transdermal device may alternatively be of a more simple construction wherein the polymer matrix containing the pharmaceutical composition additionally comprises an adhesive. In such a simple construction there is no need for the layers of the aforementioned adhesive in order to fix and releasably fix respectively the backing layer and release-liner as the polymer matrix containing the Compound A is self adhesive.

The thickness of the pharmaceutical composition layer in a transdermal device may be in the order of from 20 to 100 μm, more preferably 60 to 100.

The backing layer is preferably made of poly(ethylene terephthalate) PET foil. The backing layer should be thick enough to resist wrinkling which may arise upon prolonged periods in storage and through the movement of a subject's skin. Typically, the backing layer is, e.g. from approximately 10 μm to 15 μm, in thickness.

In a preferred embodiment, the backing layer is a double layer which consists of a PET layer as aforementioned and an EVA layer, e.g. Scotch Pack 1012.

The release-liner may be a disposable element which serves to protect the pharmaceutical composition prior to its application. Typically the release-liner is produced from a material impermeable to compound A, and adhesive. This release-liner may be easily stripped away from the adhesive. A preferred release-liner is made of poly(ethylene terephthalate) PET foil. A release-liner, e.g. of about 50 to 250 μm, e.g. 100 μm thickness PET film, may be applied over the pharmaceutical composition.

The release liner may be silicone-coated. Said coating is preferably formed of any fluorosilicone compound which is conventionally used in the art, e.g a polyfluoroalkylsiloxane.

It is particularly preferred to employ such a fluorosilicone coating when the adhesive used to affix the pharmaceutical composition to the release liner is not itself a silicone adhesive.

The adhesive may be chosen from any adhesive suitable for skin contact and is preferably an adhesive in which Compound A dissolves at least partly. Preferably the adhesive is a contact adhesive which is pressure sensitive. Preferred adhesive are chosen from amine-resistant silicone pressure sensitive adhesives known in the art, for example the BIO-PSA adhesives produced by Dow Corning Corporation, in particular BIO-PSA Q7-4302.

In a very simple construction of the transdermal device, the adhesive may in fact be the polymer of the polymer matrix.

In a further embodiment, the invention provides a transdermal device comprising a backing layer, a layer comprising compound A in a polymer matrix, a release-liner and, disposed between the layer comprising compound A in a polymer matrix and the release liner, a discrete layer of adhesive material for releasably fixing said transdermal device to patients skin.

Preferably, the adhesive material is a silicone adhesive chosen from amine-resistant silicone pressure sensitive adhesives as hereinabove described.

Typically, a transdermal device of said further embodiment comprises:

a) a polymethacrylate backing layer

b) Compound A in free base form in an acrylate copolymer

c) a BIO-PSA Q7-4302 silicone adhesive layer

d) a release-liner.

Preferably, said further embodiment also comprises silicone oil, e.g. silicone oil Q7-9120 from Dow Corning Corporation, in an amount of 0.1 to 5% by weight, e.g. 1%. The backing layer thickness is preferably from 10 to 50 μm, e.g. 23 μm, and has preferably a round shape.

In general transdermal devices of the invention may be produced in a simple manner. A solvent-evaporation process may be used for said compositions. Thus all the ingredients of the pharmaceutical composition may be mixed in a solvent, e.g. acetone, ethylacetate or hexane, and cast onto a substrate which may act as the backing layer or the release-liner.

The transdermal device aforementioned may be conveniently formed in continuous sheets and may be cut into patches of any desirable size or configuration before use. However, the patches so-formed may expose the pharmaceutical composition-containing layer of the laminate to the atmosphere at the outer edges of the patch.

In an alternative embodiment, however, a transdermal device is provided wherein in the patches formed therefrom, the pharmaceutical composition is not exposed to the atmosphere during storage or during application. Such patches further reduce the likelihood of the Compound A being exposed to oxidative influences. The transdermal device may comprise, e.g. a continuous backing layer, a continuous release-liner and located there-between, in discrete portions, a pharmaceutical composition portion, the backing layer being configured such that it may be releasably fixed with an adhesive to the release-liner so to seal said pharmaceutical composition in a pocket defined by the inner surface of the backing layer and inner surface of the release-liner. This embodiment may be conveniently referred to as a cover patch.

The pocket described hereinabove is preferably filled with an adhesive so as to encapsulate completely the discrete portion of pharmaceutical composition. Preferably the adhesive is a silicone pressure sensitive adhesive as described hereinabove.

It is an optional feature of all the transdermal devices described hereinabove that they comprise a layer of adhesive between the pharmaceutical composition and the release liner. This, has the primary function of fixing the release liner in contact with the remainder of the device thus protecting the pharmaceutical composition before use. However, if the adhesive is a silicone adhesive, then the layer may additionally act as a membrane through which the Compound A may pass at a controlled rate into the patient through the skin. Without wishing to be limited to a particular theory, it is suggested that the Compound A, dispersed throughout the polymer matrix exhibits little tendency to migrate into the silicone adhesive layer during storage. Accordingly, there is relatively low concentration of Compound A in the silicone layer. In use, the subjects skin, however, may display a much higher affinity for Compound A than the silicone layer and the initial low concentration of Compound A in the silicone layer passes into the subject's body. The silicone layer surprisingly prevents the subject from receiving a sudden high dose of Compound A upon application of the device and instead promotes a gradual increase of concentration in the subject.

The cover patch transdermal device may conveniently be formed as a continuous sheet or webbing and may be cut, or tom along a frangible area dividing each device, into patches before use although such devices may be provided as discrete patches.

The transdermal devices of the invention in general have, for example an effective contact area of pharmaceutical composition on the skin of from about 1 to about 80 square centimeters, preferably about 10 square centimeters, and are intended to be applied at intervals of about once every 1 to 7 days, preferably 1–3 days. Compound A is well tolerated at a dose of 36 mg in free base form in up to 80 cm^2 of patches according to the invention containing 36 mg compound A from which 12 mg was absorbed. Compound A may, for example be administered at a dose of 8 mg in a patch of ca. 10 cm^2, once every day. The patch may be applied, for example on the abdomen, thigh, behind an ear, or on a shoulder or upper arm.

The pharmaceutical composition, optionally formed as a transdermal device, of the present invention are useful for the same indications as for known compositions containing compound A. The exact amounts of compound A to be administered may depend on a number of factors, e.g. the drug release characteristics of the compositions, the drug penetration rate observed in vitro and in vivo tests, the duration of action required, the form of compound A, and for transdermal compositions the size of the skin contact area,

and the part of the body to which the unit is fixed. The amount of and, e.g. area of the composition etc. may be determined by routine bioavailability tests comparing the blood levels of active agents after administration of compound A in a composition according to the invention to intact skin and blood levels of Compound A observed after oral administration of a therapeutically effective dose of the compound.

Orally, the Compound A is well tolerated at an initial dose of 1.5 mg twice a day orally and the dose may be stepped up to 3 mg twice daily in week 2. Higher dosages are possible, for example 4.5 mg twice daily and even 6 mg twice daily. Tolerability is seen to be even better for the transdermal device, wherein 24 mg were absorbed in 24 hours.

The following example illustrates the invention.

EXAMPLE 1

A composition is prepared consisting of the following components (by weight)

	(I)	(II)
Compound A	30%	30%
Polymer	20% (A)	20% (D)
Methacrylate	49.85% (B)	49.85% (C)
α-tocopherol	0.15%	0.15%

The components are added to ethyl acetate and mixed to give a viscous mass. The mass is spread onto a 100 μm transparent PET foil to produce a film 60 μm thick. A 15 μm thick PET foil release-liner is applied onto the dried mass. The patch is cut up into patches 10, 20, 30 or 40 cm^2 in area.

The liner is removed before application to the skin.

The compositions and devices of this invention provide storage stable systems. Insignificant degradation is detected after storage of up to 6 months at room temperature.

EXAMPLE 2

A composition is prepared according to Example 1 with Ascorbyl-palmitate instead of α-tocopherol. Insignificant amounts of degradation products are detected after storage of at least four months at room temperature.

EXAMPLE 3

A composition is prepared according to Example 1 with a mixture of Ascorbyl-palmitate and α-tocopherol instead of α-tocopherol alone. Insignificant amounts of degradation products are detected after storage of at least four months at room temperature.

EXAMPLE 4

A two-parts composition is prepared consisting of the following components

	Composition per unit (10 cm^2)	
Compound A	18 mg	30%
Polymer	29.94 mg	49.85%
Methacrylate	12 mg	20%
α-tocopherol	0.06	0.1%
Total 1st part (area weight 60 mg/10 cm^2)	70 mg	100%

-continued

	Composition per unit (10 cm^2)	
and		
Bio-PSA Q7-4302	29.67 mg	98.9%
Silicone oil Q7-9120	0.3 mg	1.0%
α-tocopherol	0.03 mg	0.1%
Total 2nd part (area weight 30 mg/10 cm^2)	30 mg	100%

The two parts are then put together in the form of a patch.

What is claimed is:

1. A pharmaceutical composition comprising:

(a) a therapeutically effective amount of (S)-N-ethyl-3-{(1-dimethylamino)ethyl}-N-methyl-phenyl-carbamate in free base or acid addition salt form (Compound A);

(b) about 0.01 to about 0.5 percent by weight of an antioxidant, based on the weight of the composition, and

(c) a diluent or carrier.

2. A pharmaceutical composition according to claim **1** containing 1 to 40% by weight of Compound A in free base or acid addition salt form.

3. A pharmaceutical composition according to claim **1** wherein the anti-oxidant is tocopherol, esters thereof, ascorbic acid, butylhydroxytoluene, butylhydroxyanisole or propyl gallate.

4. A pharmaceutical composition according to claim **1** wherein the anti-oxidant is α-tocopherol or ascorbyl palmitate.

5. A pharmaceutical composition according to claim **1** wherein the anti-oxidant is tocopherol and is present in an amount of 0.1% by weight based on the weight of the pharmaceutical composition.

6. A pharmaceutical composition according to claim **1** comprising

(a) Compound A in free base form in an amount of 20 to 40% by weight,

(b) polymethacrylate in an amount of 10 to 30% by weight,

(c) acrylate copolymer in an amount of 40 to 60% by weight, and

(d) α-tocopherol in an amount of between 0.05 and 0.3% by weight

wherein the total weight of the pharmaceutical composition is 100%.

7. A transdermal device comprising a pharmaceutical composition as defined in claim **1**, wherein the pharmaceutical composition is supported by a substrate.

8. A transdermal device according to claim **7**, wherein the pharmaceutical composition is located between an adhesive layer and the substrate.

9. A transdermal device according to claim **8**, wherein a release liner releasably contacts the adhesive layer.

10. The pharmaceutical composition of claim **1**, further comprising silicone oil.

11. A transdermal device comprising a backing layer, a layer comprising a therapeutically effective amount of (S)-N-ethyl-3-{(1-dimethylamino)ethyl}-N-methyl-phenyl-carbamate (Compound A) and an amount of antioxidant effective to stabilize Compound A from degradation in a polymer matrix, a release-liner and, disposed between the layer comprising Compound A in a polymer matrix and the release-liner, a discrete layer of adhesive material for releasably fixing said transdermal device to a patient's skin.

12. The transdermal device of claim 1, wherein the discrete layer of adhesive material also comprises silicone oil.

13. The transdermal device of claim 1, wherein the antioxidant is tocopherol, esters thereof, ascorbic acid, butylhydroxytoluene, butylhydroxyanisole, or propyl gallate.

14. The transdermal device of claim 1, wherein the antioxidant is α-tocopherol or ascorbyl palmitate.

15. A method of stabilizing (S)-N-ethyl-3-{(1-dimethylamino)ethyl}-N-methyl-phenyl-carbamate in free base or acid addition salt form (Compound A), wherein the method comprises forming a composition by combining Compound A with an amount of anti-oxidant effective to stabilize Compound A from degradation.

16. A method according to claim 15, wherein the anti-oxidant is tocopherol, esters thereof, ascorbic acid, butylhydroxytoluene, butylhydroxyanisole or propyl gallate.

17. The method of claim 15, wherein the anti-oxidant is α-tocopherol or ascorbyl palmitate.

18. The method of claim 15, wherein the anti-oxidant is present in an amount of from about 0.01 to about 0.5% by weight based on the weight of the composition.

19. The method of claim 15, wherein α-tocopherol is present as the antioxidant in an amount of 0.1% by weight of the composition.

20. The method of claim 15, wherein the composition also comprises silicone oil.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,335,031 B1
DATED : January 1, 2002
INVENTOR(S) : Asmussen et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Title page,
Item [30], should read:
-- Jan. 12, 1998 (GB) ..... 9800526 --.

Item [56], **References Cited**, U.S. PATENT REFERENCES, should read:

-- 4,948,807	8/1990	Rosin et al.	514/484
5,344,656	9/1994	Enscore et al.	424/448
5,462,745	10/1995	Enscore et al.	424/448 --

Item [56], **References Cited**, FOREIGN PATENT REFERENCES, should read:

-- EP	427 741 B1	5/1991
WO	89/12470	12/1989 --

Column 9,
Lines 1-3, should read:

-- The transdermal device of claim 11, wherein the discrete layer of adhesive material also comprises silicone oil. --.
Lines 4-7, should read:

-- The transdermal device of claim 11, wherein the antioxidant is tocopherol, esters thereof, ascorbic acid, butylhydroxytoluene, butylhydroxyanisole, or propyl gallate. --.

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,335,031 B1
DATED : January 1, 2002
INVENTOR(S) : Asmussen et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 9, cont'd.
Lines 8-9, should read:

-- The transdermal device of claim 11, wherein the antioxidant is α-tocopherol or ascorbyl palmitate. --.

Signed and Sealed this

First Day of October, 2002

Attest:

Attesting Officer

JAMES E. ROGAN
Director of the United States Patent and Trademark Office

US006316023B1

(12) **United States Patent**
Asmussen et al.

(10) **Patent No.: US 6,316,023 B1**
(45) **Date of Patent: *Nov. 13, 2001**

(54) **TTS CONTAINING AN ANTIOXIDANT**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **09/747,519**

(22) Filed: **Dec. 20, 2000**

Related U.S. Application Data

(63) Continuation of application No. 09/291,498, filed on Apr. 14, 1999, which is a continuation-in-part of application No. PCT/EP99/00078, filed on Jan. 8, 1999.

(30) **Foreign Application Priority Data**

Jan. 12, 1998 (GB) 9800526

(51) **Int. Cl.**[7] **A61K 9/70**

(52) **U.S. Cl.** **424/449**; 424/448; 602/57; 602/60; 604/290; 604/305; 604/307

(58) **Field of Search** 424/449, 448; 602/57, 60; 604/290, 305, 307

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(74) *Attorney, Agent, or Firm*—John D. Thallemer

(57) **ABSTRACT**

Pharmaceutical composition comprising (S)-N-ethyl-3-[1-dimethylamino)ethyl]-N-methyl-phenyl-carbamate in free base or acid addition salt form and an antioxidant. Said pharmaceutical compositions may be delivered to a patient using a transdermal delivery device.

9 Claims, No Drawings

Novartis Pharmaceuticals Corp., et al. v. Par Pharmaceutical, Inc., et al.
JTX002

TTS CONTAINING AN ANTIOXIDANT

This application is a continuation of U.S. application Ser. No. 09/291,498, filed Apr. 14, 1999, which is a continuation-in-part of International Application No. PCT/EP99/00078, filed Jan. 8, 1999.

This invention relates to a pharmaceutical composition for systemic administration of a phenyl carbamate, e.g. by transdermal administration. In particular this invention relates to a pharmaceutical composition of the phenyl carbamate—(S)-N-ethyl-3-[1-dimethylamino)ethyl]-N-methyl-phenyl-carbamate—(hereinafter referred to as compound A) in free base or acid addition salt form as disclosed in published UK patent application GB 2 203 040, the contents of which are incorporated herein by reference.

Compound A is useful in inhibiting acetylcholinesterase in the central nervous system, e.g. for the treatment of Alzheimer's disease.

A transdermal composition in the form of a patch is described in Example 2 of GB 2,203,040 according to which compound A is mixed with two polymers and a plasticiser to form a viscous mass. This mass is applied to a foil which is cut into patches.

It has now been found after exhaustive testing that compound A is susceptible to degradation, particularly in the presence of oxygen. The transdermal composition described in GB 2203040 has been found to degrade, possibly by oxidative degradation, despite the formation of an occlusive polymer matrix around compound A and its storage in air-tight packaging.

The present applicant has found that stable pharmaceutical compositions comprising compound A can now be obtained, which show insignificant degradation of compound A over a prolonged time period, e.g. 2 years, as indicated by standard tests, e.g. stress tests.

In one aspect, the invention provides a pharmaceutical composition comprising Compound A in free base or acid addition salt form and an anti-oxidant.

The pharmaceutical compositions of the present invention show a reduction in degradation by-products in stress stability tests.

The pharmaceutical compositions of the invention may contain high amounts of compound A, e.g. from 1 to 40% by weight, e.g. 10–35%, more particularly 20–35%, e.g. 30%.

The compound A may be in any of a wide variety of pharmaceutical diluents and carriers known in the art. The diluent or carrier may contain trace amounts of free radicals without affecting the stability of the pharmaceutical composition of the invention.

The diluent or carrier is preferably one or more polymers, more preferably a hydrophilic polymer or polymers. In a preferred embodiment the diluent of carrier is selected from at least one polymer selected from acrylate polymers, and polymethacrylate polymers. The polymers preferably have a mean molecular weight of from about 50,000 to about 300,000 Daltons, e.g. 100,000 to 200,000 Daltons. The polymers preferably are capable of forming a film, thus to be compatible to the skin.

As a polymer one can mention in particular an acrylate co-polymer, e.g. co-polymers of butyl acrylate, ethyl hexyl acrylate and vinyl acetate. Preferably the polymer is cross-linked. A preferred acrylate polymer is one of the Durotak brand available from National Starch and Chemical Company, Zutphen, Holland, e.g. Durotak 87-2353 (hereinafter polymer A), 387-2051 or 387-2052 (hereinafter polymer D).

The diluent or carrier is preferably present in an amount of up to 90%, more preferably 70% by weight base on the total weight of the pharmaceutical composition.

The polymer, when a hydrophilic polymer, may conveniently take up water and is permeable to water, e.g. moisture from the skin, although the polymer may be insoluble in water. The polymer may swell and provide release of a large amount of pharmacologically active agent leading to a high concentration gradient of pharmacologically active agent between the skin surface and stratum corneum at a pH of from 4 to 7, preferably at skin pH, e.g. around 5.5. If desired such polymers may be soluble in organic solvents.

Examples of suitable polymers include polyacrylamide and its co-polymers, polyvinylpyrrolidone (PVP), vinyl acetate/vinyl alcohol co-polymers, polyvinyl alcohol (PVA) and derivatives, ethyl cellulose and other cellulose and starch derivatives.

Hydrophilic polyacrylates are preferred polymers. The polyacrylate may be substituted, e.g. a methacrylate. They may be commercially available acrylate/methacrylate co-polymers. Some or all of the acid groups may be esterified, e.g. with alkyl (C_{1-10}) groups, more particularly alkyl groups having 1 to 4 carbon atoms such as methyl or ethyl groups.

Examples of commercially available polymers of this type include:

1) Polymers of methacrylate containing alkyl (C_{1-4}) ester groups. Preferably the polymer matrix is a mixture of an acrylate polymer and a methacrylate polymer e.g. in a weight ratio of from 5:1 to 1:1, e.g. 4:1 to 2:1 e.g. 3:1, e.g. butylmethylacrylate and methylmethylacrylate. MW 20000, e.g. Plastoid B from Röhm, Darmstadt, Germany (hereinafter polymer B).

2) Polymers of acrylate and methacrylate esters containing methyl and ethyl neutral ester groups and trimethylaminoethyl cationic ester groups. Chloride ions may be present. Mean Molecular weight 150000 Daltons. Viscosity (20° C.), maximum 15 cP. Refractive index 1.380–1.385. Density 0.815–0.835 g/cm^3. Ratio of cationic ester groups to neutral alkyl groups 1:20 giving an alkali count of 28.1 mg KOH per gram polymer (Eudragit RL 100 Registered Trade Mark available from Röhm) or 1:40 giving an alkali count of 15.2 mg KOH per gram polymer (Eudragit RS 100 Registered Trade Mark, also available from Röhm).

3) Polymers of methacrylate esters containing trimethylaminoethyl cationic ester groups and other neutral (C_{1-4})alkyl ester groups. Chloride ions may be present. Mean molecular weight 150,000. Viscosity (20° C.) 10 cP. Refractive Index 1.38. Density 0.815. Alkali number of 180 mg KOH per gram polymer (Eudragit E 100, Registered Trade Mark, also available from Röhm and hereinafter referred to a polymer C).

If desired the pharmaceutical composition may contain other additives, such as plasticizers and/or softeners preferably skin compatible tensides, e.g. to provide flexibility to the pharmaceutical composition, and/or to dissolve partially or totally compound A.

Examples of additives include:

1) Polyoxyethylene fatty alcohol ethers. The alcohol may e.g. be a C_{12-18} alcohol. The HLB value may be e.g. from 10 to 18. A preferred example is polyoxyethylene-(10) oleyl ether. A suitable ether may have a viscosity (25° C.) of about 100 cP, a solidification point of about 16° C., an HLB value of 12.4 and an acid count maximum 1.0 (Brij 97 Registered Trade Mark available from Atlas Chemie, Germany).

2) Polyoxyethylene Sorbitan fatty acid esters. The fatty acid may be e.g. a C_{12-18} fatty acid. The HLB value

may be e.g. from 10 to 18. A preferred example is polyoxyethylene-(20) sorbitan monooleate, e.g. Tween 80, Registered Trade Mark available from Atlas Chemie, Germany.

3) Polyoxyethylene-(5-40) stearic acid esters, e.g. Myrj (Registered Trade Mark) available from Atlas Chemie, Germany.

4) Polyoxyethylene glycol fatty alcohol ethers, e.g. polyethylene glycol-(6-25) cetyl ether, glycerin polyethylene ricinoleate, glycerin polyethylene glycol stearate (Cremophor brand, Registered Trade Mark available from BASF Germany).

5) Polyoxyethylene glycols of MW from 200 to 600 Daltons, e.g. 300 or 400 Daltons.

6) Esters of poly(2-7)ethylene glycol glycerol ether having at least one hydroxyl group and an aliphatic (C_{6-22}) carboxylic acid, e.g. Polyethylene glycol-(7) glyceryl cocoate, e.g. Cetiol HE, Registered Trade Mark, from Henkel, Germany.

7) Adipic acid lower alkyl esters, e.g. di-n-butyl adipate and diisopropyl adipate.

8) Glycerin polyethylene glycol ricinoleate, e.g. Product of 35 moles ethylene oxide and castor oil, e.g. Brand Cremophor EL Registered Trade Mark, obtainable from BASF, Germany.

9) Triacetin-(1,2,3).

10) Fatty acid, e.g. a C_{12-18} fatty acid.

11) Fatty alcohol, e.g. a C_{12-18} fatty alcohol.

The amount and type of additive required may depend on a number of factors, e.g. the HLB value of the tenside and the flexibility of the pharmaceutical required. The amount of additive does not significantly influence the capability of the polyacrylate to form films. Generally the weight ratio of tenside to the polymer may be from about 1:10 to 5:1, e.g. 1:10 to 1:3.

Preferably, however, no such additive is present or is only present in an amount less than 1% by weight based on the total weight of the pharmaceutical composition.

The pharmaceutical composition may contain skin penetration promoters, e.g. 1-dodecylazacycloheptan-2-one (azone) and N,N-diethyl-m-toluamide (DEET).

The amount and type of skin penetration promoter, and/or additives present may depend on a number of factors. Generally the weight ratio of skin penetration promoting agent to hydrophilic polymer will be from about 1:1 to 1:10. Preferably the amount of tenside and/or skin penetration promoter may be from about 3 to about 50%, preferably 20 to 40% by weight of the pharmaceutical composition.

Preferably however no such additive is present or is only present in an amount less than 1% by weight of the pharmaceutical composition.

If desired the pharmaceutical composition may contain a hydrophobic elastomer, e.g. a synthetic resin. Such resins are conventional in the plaster art. Suitable resins may include non-swellable acrylate resins. These may if desired be adhesive. The weight ratio of polymer, e.g. hydrophilic polymer to resin may for example be from 1:0.5 to 1:10. The resin may contain modifiers, extenders, e.g. of softening point about 50 to 100° C. Such extenders may have adhesive or softening properties. Examples of such extenders may include resin acids, glyceryl and phthalate esters of resin acids.

A preferred pharmaceutical composition according to the invention comprises

a) (S)-N-ethyl-3-[1-dimethylamino)ethyl]-N-methyl-phenyl-carbamate as compound A in free base form in an amount of 20 to 40 weight-%,

b) polymethacrylate in an amount of 10 to 30% by weight

c) acrylate copolymer in an amount of 40 to 60% by weight, and

d) α-tocopherol in an amount of between 0.05 and 0.3% by weight

wherein the total weight of the pharmaceutical composition is 100%.

In another aspect the present invention provides the use of an anti-oxidant to stabilize a pharmaceutical composition containing Compound A.

Before the finding by the present applicant that an anti-oxidant is necessary in compositions of this invention, it was hitherto thought unnecessary.

The applicant has found that an effective stabilising effect is surprisingly achieved when the anti-oxidant is selected from tocopherol, esters thereof, e.g. tocopherol acetate, ascorbyl palmitate, ascorbic acid, butylhydroxytoluene, butylhydroxyanisole or propyl gallate, preferably α-tocopherol or ascorbyl palmitate. The antioxidant may be conveniently present in an amount of from about 0.01 to about 0.5%, e.g. 0.05 to 0.20, e.g. 0.15%, more particularly 0.1% by weight based on the total weight of the pharmaceutical composition.

Pharmaceutical compositions of the invention produced in analogous manner to example 1 described hereinafter containing 0.1% tocopherol show for Example only 1.3% degradation products compared to 4.46% degradation products in equivalent compositions not containing tocopherol in 2 month stress tests at 60° C. Pharmaceutical compositions of the invention in analogous manner to example 1 described hereinafter containing 0.15% tocopherol show for example only 0.25% degradation products compared to 1.09% degradation products in compositions not containing tocopherol in 3 month stress tests at 40° C. at 75% room humidity.

The pharmaceutical composition of the invention is preferably used for transdermal application.

In another aspect of the invention there is provided a transdermal device for administering a Compound A which comprises a pharmaceutical composition containing Compound A, a backing layer providing support for the pharmaceutical composition, an adhesive for fixing the pharmaceutical composition to the backing layer and a release-liner releasably contacting said adhesive.

The pharmaceutical composition may be conveniently contained in a discrete thin layer, the upper and lower surfaces of which may be coated in a layer of adhesive the surface of which in turn provide backing layer and release-liner contacting surfaces.

The pharmaceutical composition contained in the discrete layer may comprise the Compound A and other excipients in a polymer matrix, the polymer matrix therefor being provided by the diluent or carrier aforementioned. If desired Compound A may be dispersed throughout, or dissolved in, said polymer matrix.

The transdermal device may alternatively be of a more simple construction wherein the polymer matrix containing the pharmaceutical composition additionally comprises an adhesive. In such a simple construction there is no need for the layers of the aforementioned adhesive in order to fix and releasably fix respectively the backing layer and release-liner as the polymer matrix containing the Compound A is self adhesive.

The thickness of the pharmaceutical composition layer in a transdermal device may be in the order of from 20 to 100 μm, more preferably 60 to 100.

The backing layer is preferably made of poly(ethylene terephthalate) PET foil. The backing layer should be thick

enough to resist wrinkling which may arise upon prolonged periods in storage and through the movement of a subject's skin. Typically, the backing layer is, e.g. from approximately 10 μm to 15 μm, in thickness.

In a preferred embodiment, the backing layer is a double layer which consists of a PET layer as aforementioned and an EVA layer, e.g. Scotch Pack 1012.

The release-liner may be a disposable element which serves to protect the pharmaceutical composition prior to its application. Typically the release-liner is produced from a material impermeable to compound A, and adhesive. This release-liner may be easily stripped away from the adhesive. A preferred release-liner is made of poly(ethylene terephthalate) PET foil. A release-liner, e.g. of about 50 to 250 μm, e.g. 100 μm thickness PET film, may be applied over the pharmaceutical composition.

The release liner may be silicone-coated. Said coating is preferably formed of any fluorosilicone compound which is conventionally used in the art, e.g a polyfluoroalkylsiloxane.

It is particularly preferred to employ such a fluorosilicone coating when the adhesive used to affix the pharmaceutical composition to the release liner is not itself a silicone adhesive.

The adhesive may be chosen from any adhesive suitable for skin contact and is preferably an adhesive in which Compound A dissolves at least partly. Preferably the adhesive is a contact adhesive which is pressure sensitive. Preferred adhesive are chosen from amine-resistant silicone pressure sensitive adhesives known in the art, for example the BIO-PSA adhesives produced by Dow Coming Corporation, in particular BIO-PSA Q7-4302.

In a very simple construction of the transdermal device, the adhesive may in fact be the polymer of the polymer matrix.

In a further embodiment, the invention provides a transdermal device comprising a backing layer, a layer comprising compound A in a polymer matrix, a release-liner and, disposed between the layer comprising compound A in a polymer matrix and the release liner, a discrete layer of adhesive material for releasably fixing said transdermal device to patients skin.

Preferably, the adhesive material is a silicone adhesive chosen from amine-resistant silicone pressure sensitive adhesives as hereinabove described.

Typically, a transdermal device of said further embodiment comprises:

a) a polymethacrylate backing layer

b) Compound A in free base form in an acrylate copolymer

c) a BIO-PSA Q7-4302 silicone adhesive layer

d) a release-liner.

Preferably, said further embodiment also comprises silicone oil, e.g. silicone oil Q7-9120 from Dow Coming Corporation, in an amount of 0.1 to 5% by weight, e.g. 1%. The backing layer thickness is preferably from 10 to 50 μm, e.g. 23 μm, and has preferably a round shape.

In general transdermal devices of the invention may be produced in a simple manner. A solvent-evaporation process may be used for said compositions. Thus all the ingredients of the pharmaceutical composition may be mixed in a solvent, e.g. acetone, ethylacetate or hexane, and cast onto a substrate which may act as the backing layer or the release-liner.

The transdermal device aforementioned may be conveniently formed in continuous sheets and may be cut into patches of any desirable size or configuration before use. However, the patches so-formed may expose the pharmaceutical composition-containing layer of the laminate to the atmosphere at the outer edges of the patch.

In an alternative embodiment, however, a transdermal device is provided wherein in the patches formed therefrom, the pharmaceutical composition is not exposed to the atmosphere during storage or during application. Such patches further reduce the likelihood of the Compound A being exposed to oxidative influences. The transdermal device may comprise, e.g. a continuous backing layer, a continuous release-liner and located there-between, in discrete portions, a pharmaceutical composition portion, the backing layer being configured such that it may be releasably fixed with an adhesive to the release-liner so to seal said pharmaceutical composition in a pocket defined by the inner surface of the backing layer and inner surface of the release-liner. This embodiment may be conveniently referred to as a cover patch.

The pocket described hereinabove is preferably filled with an adhesive so as to encapsulate completely the discrete portion of pharmaceutical composition. Preferably the adhesive is a silicone pressure sensitive adhesive as described hereinabove.

It is an optional feature of all the transdermal devices described hereinabove that they comprise a layer of adhesive between the pharmaceutical composition and the release liner. This, has the primary function of fixing the release liner in contact with the remainder of the device thus protecting the pharmaceutical composition before use. However, if the adhesive is a silicone adhesive, then the layer may additionally act as a membrane through which the Compound A may pass at a controlled rate into the patient through the skin. Without wishing to be limited to a particular theory, it is suggested that the Compound A, dispersed throughout the polymer matrix exhibits little tendency to migrate into the silicone adhesive layer during storage. Accordingly, there is relatively low concentration of Compound A in the silicone layer. In use, the subjects skin, however, may display a much higher affinity for Compound A than the silicone layer and the initial low concentration of Compound A in the silicone layer passes into the subject's body. The silicone layer surprisingly prevents the subject from receiving a sudden high dose of Compound A upon application of the device and instead promotes a gradual increase of concentration in the subject.

The cover patch transdermal device may conveniently be formed as a continuous sheet or webbing and may be cut, or torn along a frangible area dividing each device, into patches before use although such devices may be provided as discrete patches.

The transdermal devices of the invention in general have, for example an effective contact area of pharmaceutical composition on the skin of from about 1 to about 80 square centimeters, preferably about 10 square centimetres, and are intended to be applied at intervals of about once every 1 to 7 days, preferably 1–3 days. Compound A is well tolerated at a dose of 36 mg in free base form in up to 80 cm^2 of patches according to the invention containing 36 mg compound A from which 12 mg was absorbed. Compound A may, for example be administered at a dose of 8 mg in a patch of ca. 10 cm^2, once every day. The patch may be applied, for example on the abdomen, thigh, behind an ear, or on a shoulder or upper arm.

The pharmaceutical composition, optionally formed as a transdermal device, of the present invention are useful for the same indications as for known compositions containing compound A. The exact amounts of compound A to be administered may depend on a number of factors, e.g. the

drug release characteristics of the compositions, the drug penetration rate observed in vitro and in vivo tests, the duration of action required, the form of compound A, and for transdermal compositions the size of the skin contact area, and the part of the body to which the unit is fixed. The amount of and, e.g. area of the composition etc. may be determined by routine bioavailability tests comparing the blood levels of active agents after administration of compound A in a composition according to the invention to intact skin and blood levels of Compound A observed after oral administration of a therapeutically effective dose of the compound.

Orally, the Compound A is well tolerated at an initial dose of 1.5 mg twice a day orally and the dose may be stepped up to 3 mg twice daily in week 2. Higher dosages are possible, for example 4.5 mg twice daily and even 6 mg twice daily. Tolerability is seen to be even better for the transdermal device, wherein 24 mg were absorbed in 24 hours.

The following example illustrates the invention.

EXAMPLE 1

A composition is prepared consisting of the following components (by weight)

	(I)	(II)
Compound A	30%	30%
Polymer	20% (A)	20% (D)
Methacrylate	49.85% (B)	49.85% (C)
α-tocopherol	0.15%	0.15%

The components are added to ethyl acetate and mixed to give a viscous mass. The mass is spread onto a 100 μm transparent PET foil to produce a film 60 μm thick. A 15 μm thick PET foil release-liner is applied onto the dried mass. The patch is cut up into patches 10, 20, 30 or 40 cm^2 in area.

The liner is removed before application to the skin.

The compositions and devices of this invention provide storage stable systems. Insignificant degradation is detected after storage of up to 6 months at room temperature.

EXAMPLE 2

A composition is prepared according to Example 1 with Ascorbyl-palmitate instead of α-tocopherol. Insignificant amounts of degradation products are detected after storage of at least four months at room temperature.

EXAMPLE 3

A composition is prepared according to Example 1 with a mixture of Ascorbyl-palmitate and α-tocopherol instead of α-tocopherol alone. Insignificant amounts of degradation products are detected after storage of at least four months at room temperature.

EXAMPLE 4

A two-parts composition is prepared consisting of the following components

	Composition per unit (10 cm^2)	
Compound A	18 mg	30%
Polymer	29.94 mg	49.85%
Methacrylate	12 mg	20%
α-tocopherol	0.06	0.1%
Total 1st part (area weight 60 mg/10 cm^2)	70 mg	100%
and		
Bio-PSA Q7-4302	29.67 mg	98.9%
Silicone oil Q7-9120	0.3 mg	1.0%
α-tocopherol	0.03 mg	0.1%
Total 2nd part (area weight 30 mg/10 cm^2)	30 mg	100%

The two parts are then put together in the form of a patch.

What is claimed is:

1. A pharmaceutical composition comprising 1 to 40 weight percent of (S)-N-ethyl-3-[(1-dimethylamino)ethyl]-N-methylphenyl carbamate in the form of a free base or acid addition salt, 0.01 to 0.5 weight percent of an antioxidant, and a diluent or carrier, wherein the weight percents are based on the total weight of the pharmaceutical composition.

2. The composition according to claim **1** wherein the antioxidant is selected from the group consisting of tocopherol, esters of tocopherol, ascorbic acid, esters of ascorbic acid, butylhydroxytoluene, butylhydroxyanisole, propyl gallate, and combinations thereof.

3. The composition according to claim **2** wherein the antioxidant is α-tocopherol or ascorbyl palmitate.

4. The composition according to claim **1** wherein the antioxidant is present in an amount of from 0.05 to 0.2 weight percent.

5. The composition according to claim **4** wherein the antioxidant is present in an amount of from 0.1 to 0.15 weight percent.

6. A pharmaceutical composition comprising 7 to 40 weight percent of (S)-N-ethyl-3-[(1-dimethylamino)ethyl]-N-methylphenyl carbamate in the form of a free base; 10 to 30 weight percent of polymethacrylate or acid addition salt; 0.05 to 0.3 weight percent of α-tocopherol, wherein the weight percents are based on the total weight of the composition.

7. A transdermal device comprising a pharmaceutical composition comprising 1 to 40 weight percent of (S)-N-ethyl-3-[(1-dimethylamino)ethyl]-N-methylphenyl carbarnate in the form of a free base or acid addition salt, 0.01 to 0.5 weight percent of an antioxidant, and a diluent or carrier, wherein the weight percents are based on the total weight of the pharmaceutical composition.

8. The transdermal device according to claim **7** further comprising an antioxidant; a backing layer providing support for the pharmaceutical composition; an adhesive for contacting and fixing the pharmaceutical composition to the backing layer; and a release liner releasably contacting said adhesive.

9. The transdermal device according to claim **7** comprising a backing layer; a layer comprising (S)-N-ethyl-3-[(1-dimethylamino)ethyl]-N-methylphenyl carbamate and an antioxidant in a polymer matrix; a release liner; and an adhesive layer between the layer comprising (S)-N-ethyl-3-[(1-dimethylamino)ethyl]-N-methylphenyl carbamate in a polymer matrix and the release liner, wherein the adhesive layer releasably fixes the transdermal device to a patients skin.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,316,023 B1
DATED : November 13, 2002
INVENTOR(S) : Asmussen et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 8,
Line 1, should read -- A pharmaceutical compostion comprising 20 to 40 --.
Line 3, should read -- Ethyl-3-[(1dimethylamino)ethyl]-N-methylphenyl carba- --.
Line 4, should read --mate in the form of a free base or acid addition salt, 0.01 to --.

Signed and Sealed this

Twenty-fifth Day of March, 2003

JAMES E. ROGAN
Director of the United States Patent and Trademark Office